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A 19-yearold man is brought to the emergency department due to weakness and confusion. Family members report that for the last 2 weeks he has experienced polyuria, polydipsia, and increased appetite. Medical history is remarkable for an appendectomy at age 12. The patient does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in his brother. Temperature is 36.7 C (98 F), blood pressure is 90/60 mm Hg, pulse is 97/min, and respirations are 22/min. On physical examination, the patient is lethargic but follows simple commands. His breath has a fruity odor. This patient is most likely deficient in a hormone that normally performs which of the following actions?

A. Activates hormonesensitive lipase

B. Decreases glucagon secretion

C. Decreases muscle glycogen synthesis

D. Increases hepatic glucose production

E. Increases renal glucose reabsorption

Submit

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A. Activates hormone-sensitive lipase (10%)
✓ B. Decreases glucagon secretion (74%)
C. Decreases muscle glycogen synthesis (3%)
D. Increases hepatic glucose production (8%)
E. Increases renal glucose reabsorption (3%)

Omitted
Correct answer
B

74%
Answered correctly

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Time Spent

06/02/2020
Last Updated

Explanation

Insulin effects		
Effect	**Target organs**	**Consequences of inadequate insulin**
↑ Glucose uptake	• Skeletal muscle • Adipose tissue	

Insulin effects		
Effect	**Target organs**	**Consequences of inadequate insulin**

↑ Glucose uptake	• Skeletal muscle
	• Adipose tissue
	• Liver
		• **Hyperglycemia**
		  ∘ Polyuria, polydipsia
		  ∘ Lethargy
		  ∘ Polyphagia or anorexia

↑ Glycogen synthesis/ ↓ glycogenolysis	• Liver	
↓ Glucagon secretion	• Pancreas (alpha cells)	
↓ Lipolysis/ ↓ ketogenesis	• Adipose tissue • Liver	• Ketosis/ketoacidosis
↑ Protein synthesis	• Muscle	• Muscle wasting, weight loss

This patient has undiagnosed type 1 diabetes mellitus and is now presenting with **diabetic ketoacidosis** (polyuria, polydipsia, altered mental status, fruity breath [exhaled ketones]). Diabetic ketoacidosis results from a **deficiency of insulin** coupled with an excess of counterregulatory hormones (ie, glucagon, epinephrine).

Blood glucose levels are normally maintained within a tight range by the opposing effects of insulin (secreted by beta cells) and glucagon (secreted by alpha cells). In the fasting state, low blood glucose levels stimulate secretion of glucagon, which increases blood glucose levels by upregulating glycogenolysis and gluconeogenesis in the liver. In contrast, insulin is released in response to high glucose levels and functions to decrease hepatic glucose production **(Choice D)** and increase glucose uptake by insulin-responsive tissues. **Insulin also suppresses glucagon** by directly acting on the alpha cells, enhancing the metabolic effects of insulin.

In type 1 diabetes mellitus, unsuppressed glucagon secretion due to insulin deficiency contributes to excess blood glucose levels.

(Choice A) In adipose tissue, hormonesensitive lipase hydrolyzes intracellular triglycerides to release free fatty acids. Hormone-sensitive lipase is activated by ACTH and epinephrine in the fasting state and is downregulated by insulin in the fed state. In untreated type 1 diabetes, the lack of

Protein synthesis	• Muscle	• Muscle wasting, weight loss

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In type 1 diabetes mellitus, unsuppressed glucagon secretion due to insulin deficiency contributes to excess blood glucose levels.

(Choice A) In adipose tissue, hormone-sensitive lipase hydrolyzes intracellular triglycerides to release free fatty acids. Hormone-sensitive lipase is activated by ACTH and epinephrine in the fasting state and is downregulated by insulin in the fed state. In untreated type 1 diabetes, the lack of insulin induces a catabolic state, resulting in increased lipolysis; patients typically lose weight despite a normal or increased appetite.

(Choice C) In skeletal muscle, insulin increases glucose uptake and synthesis of glycogen, which is then available for energy production during exercise. Insulin also increases amino acid transport and ribosomal translation efficiency in muscle tissue, leading to an overall increase in protein synthesis. Insulin deficiency in type 1 diabetes leads to decreased muscle glycogen synthesis and muscle wasting.

(Choice E) In the renal tubules, glucose is actively taken up from the tubular lumen by sodium-glucose co-transporter 2 (SGLT2) and then passed across the basolateral membrane. This occurs independent of insulin levels and leads to near-complete reabsorption of filtered glucose (unless severe hyperglycemia overwhelms the reabsorptive capacity, leading to osmotic diuresis and polyuria).

Educational objective:
Normal blood glucose levels are maintained by the opposing effects of insulin and glucagon. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis, whereas insulin increases peripheral glucose uptake and inhibits lipolysis and ketoacid formation. Insulin also suppresses glucagon release.

References

• Minireview: glucagon in the pathogenesis of hypoglycemia and hyperglycemia in diabetes

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References

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Physiology	Endocrine, Diabetes & Metabolism	Diabetic ketoacidosis
Subject	System	Topic

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A 43-yearold woman comes to the office due to increasing fatigue and weight gain despite decreased food intake. She states, "I have not been feeling like myself lately." The patient asks to be referred to a dermatologist as she has always had "nice" skin that has now become dry. Her hair has been thinning and she hopes that a dermatologist can help with that too. Laboratory evaluation shows high serum TSH, low triiodothyronine (T3), and low thyroxine (T4) levels. The patient has a family member with fatigue whose energy level increased after liothyronine (T3) supplementation, and she asks to try this medication. Administering this therapy would most likely result in which of the following hormone level changes in this patient?

	TSH	T3	Reverse T3	T4
A.	No change	Increase	Increase	Decrease
B.	No change	Increase	Decrease	Decrease
C.	Decrease	Increase	Increase	Decrease
D.	Decrease	Increase	Decrease	Decrease
E.	Decrease	Increase	Decrease	Increase

Submit

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	TSH	T3	Reverse T3	T4
A. (3%)	No change	Increase	Increase	Decrease
B. (4%)	No change	Increase	Decrease	Decrease
C. (26%)	Decrease	Increase	Increase	Decrease
✓ D. (48%)	Decrease	Increase	Decrease	Decrease
E. (17%)	Decrease	Increase	Decrease	Increase

Omitted
Correct answer
D

48%
Answered correctly

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02/11/2020
Last Updated

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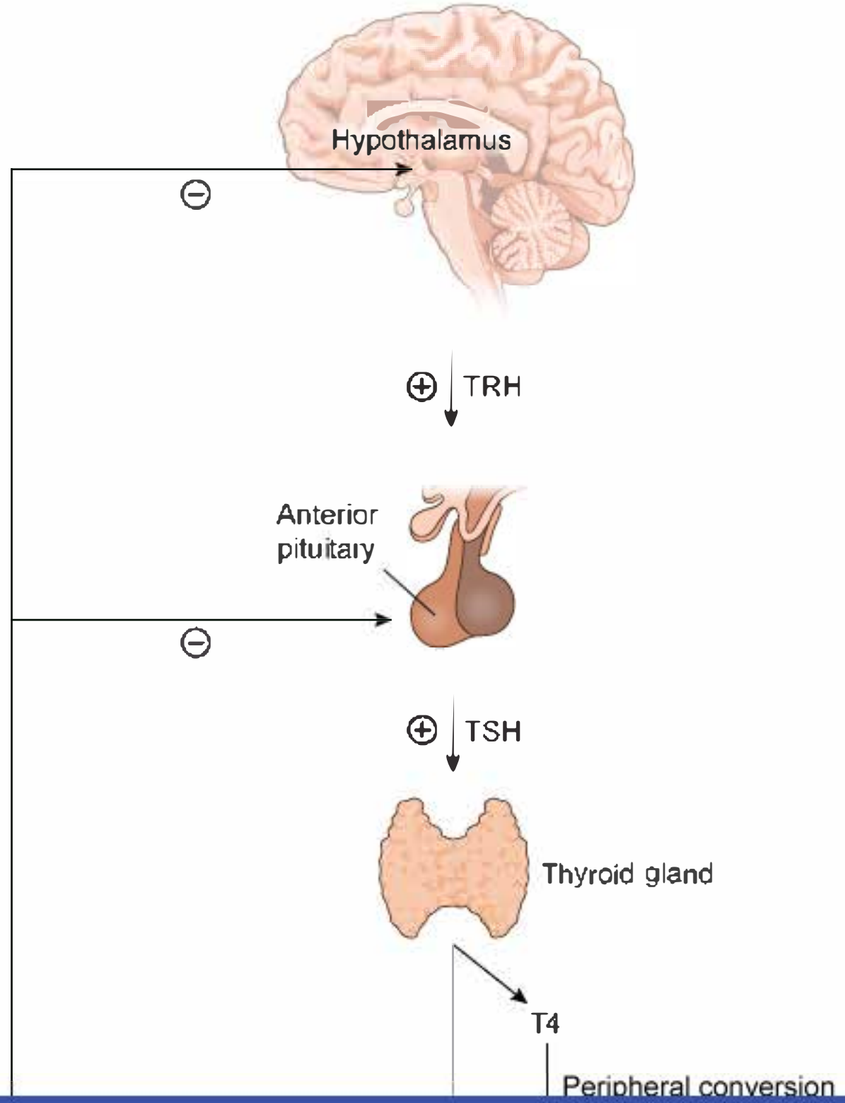
Hypothalamic-pituitary-thyroid axis



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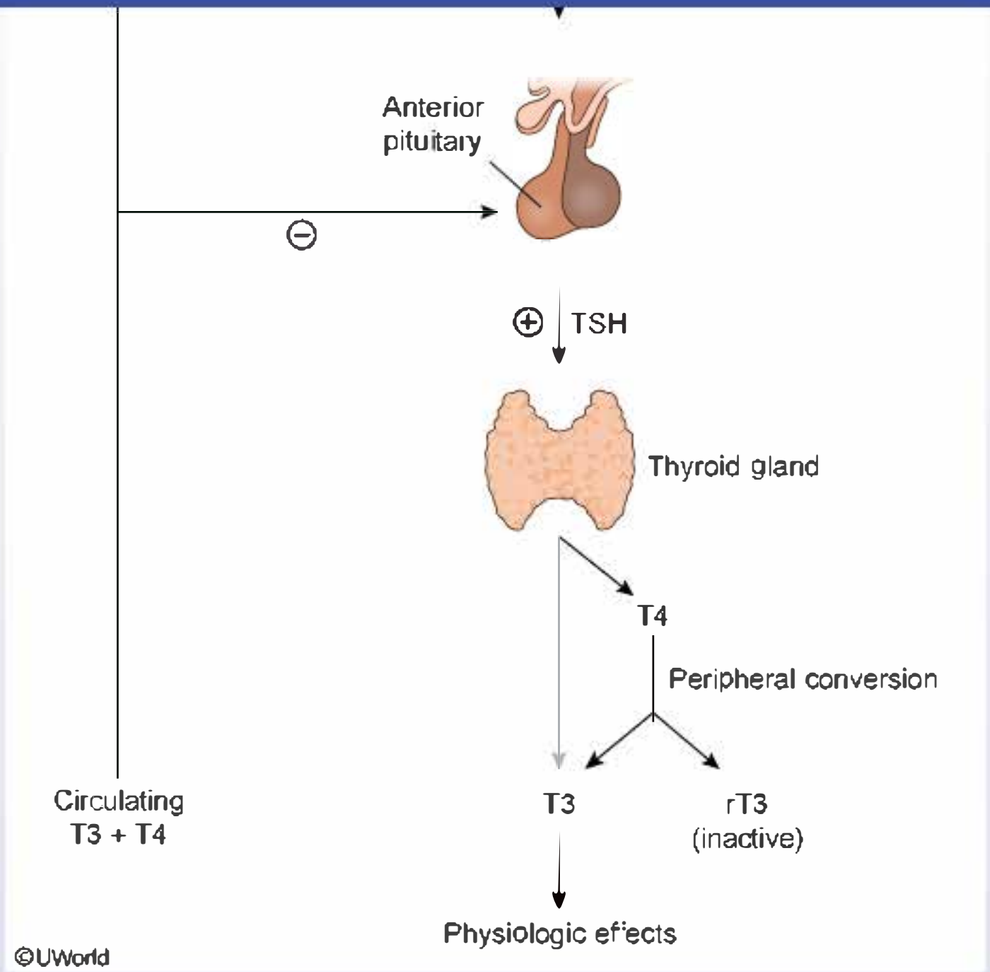

Circulating thyroid hormone exists in 3 primary forms:

1. **T4 (thyroxine)** is the major secretory product of the thyroid gland.
2. **T3 (triiodothyronine)** is the most active form of thyroid hormone; a small amount is released by the thyroid gland, but the majority arises from peripheral deiodination of T4.
3. **Reverse T3 (rT3)** is an inactive form that is generated almost entirely from the peripheral conversion of T4.

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3. **Reverse T3 (rT3)** is an inactive form that is generated almost entirely from the peripheral conversion of T4.

The hypothalamus-pituitary-thyroid axis is regulated via **negative feedback** by thyroid hormone on thyrotropin-releasing hormone–secreting neurons in the hypothalamus and thyrotrophs of the anterior pituitary. In the normal state, most of the circulating thyroid hormone is in the form of T4, which provides most of the feedback suppression of TSH release. However, T3 also suppresses TSH.

This patient has primary hypothyroidism, with low thyroid hormone (T3 and T4) and elevated TSH levels. Exogenous T3 supplementation **rapidly suppresses TSH** levels by increasing negative feedback, which in turn decreases T4 secretion from the thyroid gland. Furthermore, rT3 also decreases because less T4 is available for conversion (T3 cannot be converted into rT3).

However, synthetic T3 (liothyronine) is not recommended for the routine treatment of hypothyroidism, as it has a short half-life and patients can experience wide fluctuations in plasma T3 levels. T4 (levothyroxine) supplementation provides a more physiologic effect and is preferred.

Educational objective:

TSH from the anterior pituitary stimulates the thyroid to produce thyroxine (T4) and a small amount of triiodothyronine (T3). T4 is converted in peripheral tissues to T3 (active form) and reverse T3 (inactive form). TSH secretion is under negative feedback by thyroid hormone on the hypothalamus and pituitary.

References

- Mini review: thyrotropin-releasing hormone and the thyroid hormone feedback mechanism.

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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A 19-year-old man comes to the office due to frequent episodes of disorientation, palpitations, tremulousness, and excessive sweating over the past 3 months. He says the symptoms resolve quickly after drinking some juice or a carbonated beverage. The patient was diagnosed with type 1 diabetes mellitus at age 12 and takes short- and long-acting insulin. He has had no dose changes in the past 2 years or diabetic complications and follows up with an ophthalmologist frequently. The patient is a college student and reports some stress due to an upcoming midterm examination. He does not use tobacco, alcohol, or illicit drugs. Vital signs and physical examination are within normal limits. Laboratory results show a hemoglobin A1c of 6.8% and no proteinuria. Which of the following factors most likely precipitated this patient's current symptoms?

- A. Fructose-rich drink consumption
- B. Intense exercise
- C. Mental stress
- D. Respiratory infection
- E. Sleep deprivation
- F. Weight gain

Submit

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- A. Fructose-rich drink consumption (3%)
- ✓ B. Intense exercise (32%)
- C. Mental stress (43%)
- D. Respiratory infection (2%)
- E. Sleep deprivation (15%)
- F. Weight gain (2%)

Omitted
Correct answer
B

32%
Answered correctly

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Time Spent

05/24/2020
Last Updated

Explanation

Effect of exercise on insulin & glucose

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Effect of exercise on insulin & glucose

Normal state	Insulin-treated state
Skeletal muscle contraction	Skeletal muscle contraction
↑Glucose uptake by muscle cells	↑Glucose uptake by muscle cells
↓ Insulin release ↑ Counterregulatory hormones	Insulin levels not physiologically regulated
↑ Endogenous glucose production Limits muscle glucose uptake	Impaired endogenous glucose production Persistently high muscle glucose uptake
Glucose levels maintained	Risk of hypoglycemia

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This patient has frequent symptomatic **hypoglycemia**—disorientation, sweating, and palpitations, which are relieved by intake of glucose—despite no changes to his chronic insulin regimen. Hypoglycemia is often induced in patients with type 1 diabetes by inadvertent overdose of insulin or decreased carbohydrate intake (eg, skipped meal), but can also be triggered by **intensive physical activity/exercise**.

Glucose uptake by skeletal muscle cells is mediated by glucose transporter type 4 (**GLUT4**). GLUT4 is **translocated to cell membranes** and transverse tubules (deep invaginations in the cell membrane) in response to **insulin**. GLUT4 translocation also occurs during **muscle contraction** by an insulin-independent mechanism, which is mediated by several cellular factors, including AMP-activated kinase, nitric oxide, and calcium-calmodulin–activated protein kinase.

In normal individuals, overt hypoglycemia does not occur with exercise because a drop in blood glucose suppresses insulin release from the beta cells, and counterregulatory hormones (eg, glucagon) increase endogenous glucose production via glycogenolysis and gluconeogenesis. However, patients taking **exogenous insulin** are vulnerable to exercise-induced hypoglycemia because insulin will **continue to be released** from the injection site despite falling glucose levels.

(Choice A) Patients with hereditary fructose intolerance cannot break down fructose and develop hypoglycemia and vomiting after ingestion of fructose-containing foods. However, this typically presents at the age of weaning (when fructose is introduced) and patients often develop a protective distaste for sweets. Ingestion of fructose-containing juice and soda would worsen the hypoglycemia, not correct it.

(Choices C, D, and E) Infection, pain, sleep deprivation, and severe mental/emotional distress tend to cause hyper- rather than hypoglycemia due to increased production of counterregulatory hormones (eg, catecholamines, cortisol). These hormones raise glucose by increasing glycogenolysis and gluconeogenesis and decreasing pancreatic insulin secretion (in patients with residual islet cell function).

(Choice F) Weight gain is associated with insulin resistance. Insulin-treated patients who gain weight usually develop hyperglycemia and require increased doses of insulin to maintain control of glucose.

Educational objective:
Uptake of glucose by skeletal muscle is mediated by the glucose transporter type 4, which is translocated to the cell membrane in response to insulin and muscle contraction. Hypoglycemia can be precipitated by exercise in patients with insulin-treated diabetes due to the persistent effects of exogenous insulin.

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Uptake of glucose by skeletal muscle is mediated by the glucose transporter type 4, which is translocated to the cell membrane in response to insulin and muscle contraction. Hypoglycemia can be precipitated by exercise in patients with insulin-treated diabetes due to the persistent effects of exogenous insulin.

References

- Exercise, GLUT4, and skeletal muscle glucose uptake.

Physiology	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

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A 25-year-old man comes to the physician because he and his wife have been unable to conceive for the last 2 years. They have no children. Infertility evaluation is begun, and laboratory studies show a low sperm count. A more thorough evaluation elucidates a rare genetic abnormality that leads to permanently inactive FSH receptors. Which of the following substances is most likely decreased in this patient?

A. FSH

B. LH

C. Inhibin B

D. Testosterone

E. DHEA

Submit

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- A. FSH (1%)
- B. LH (2%)
- ✓ C. Inhibin B (79%)
- D. Testosterone (12%)
- E. DHEA (4%)

Omitted
Correct answer
C

79%
Answered correctly

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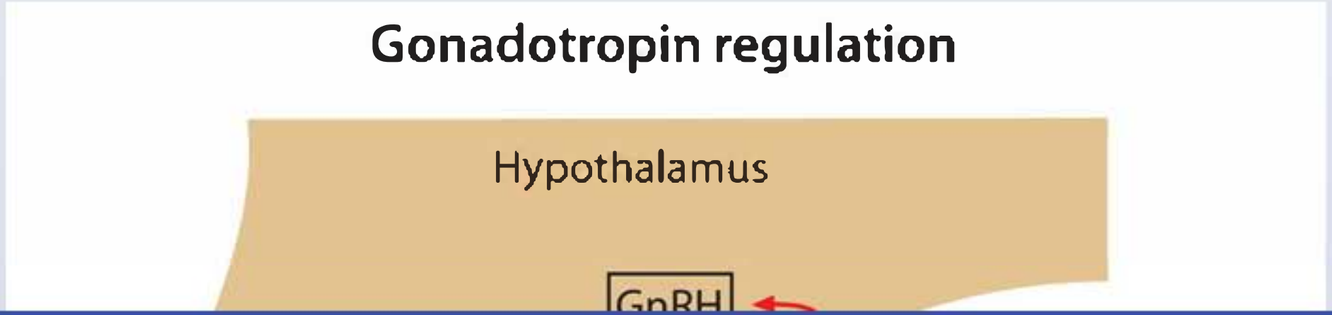
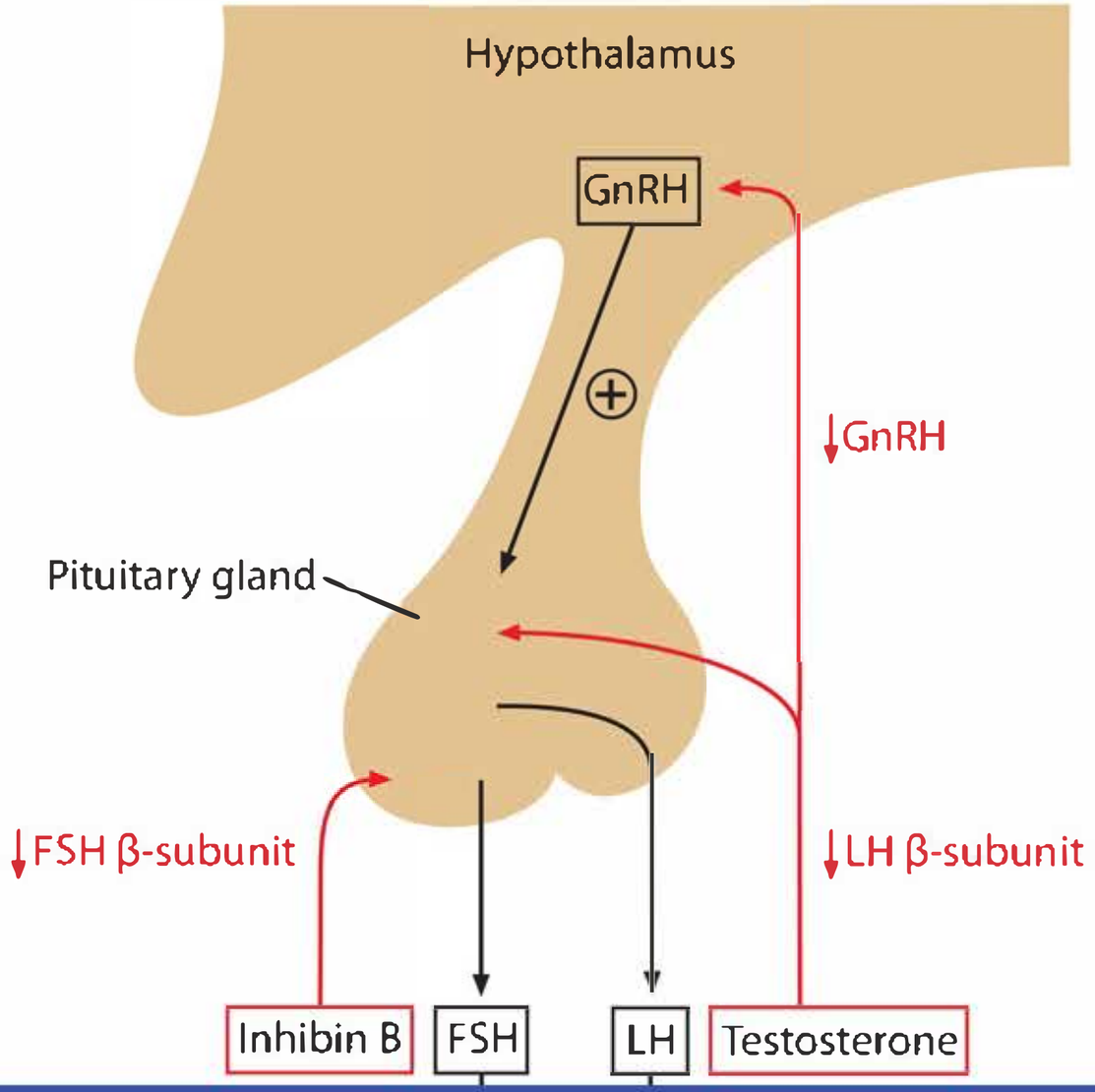
Time Spent

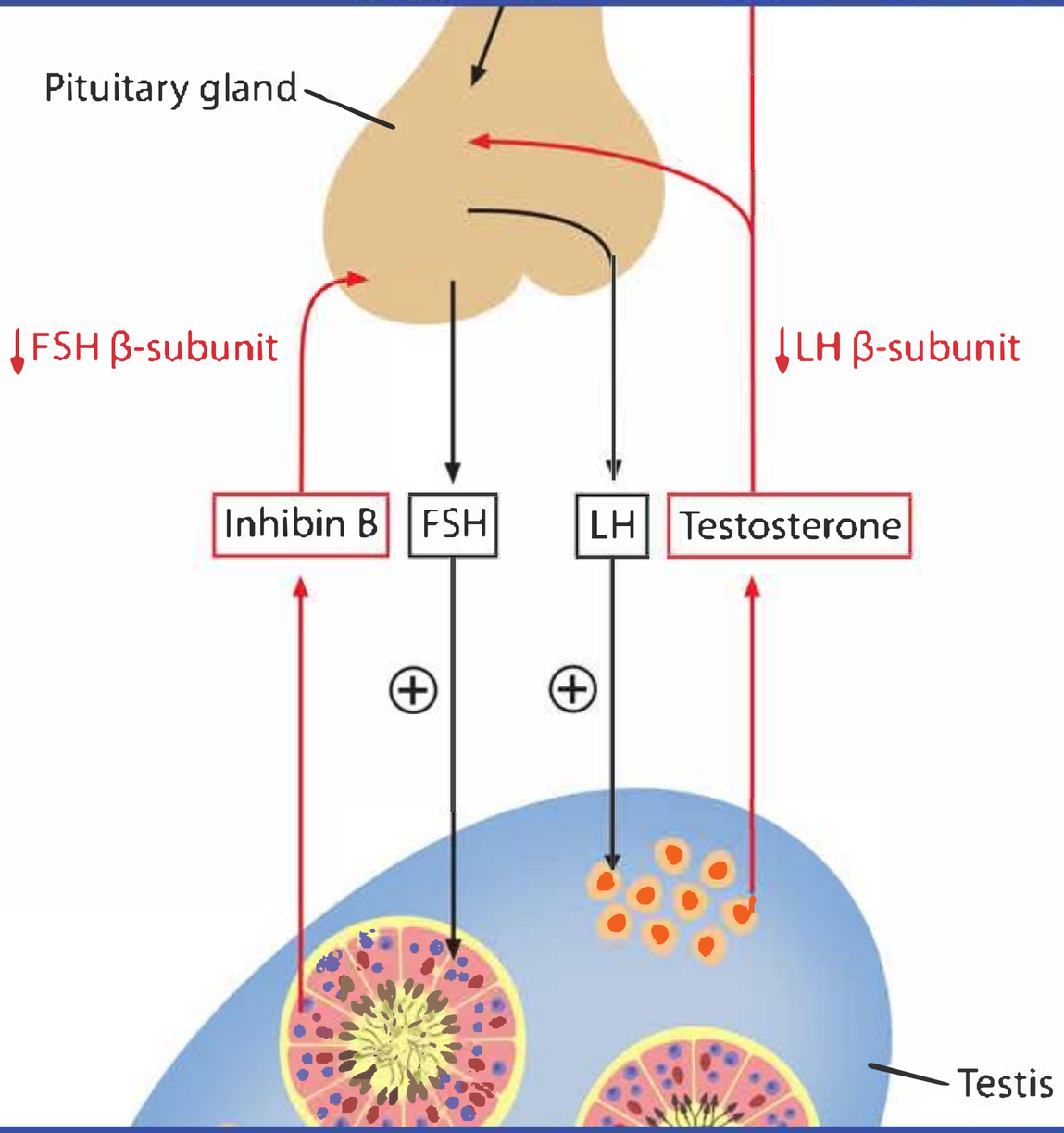
01/19/2020
Last Updated

Explanation



Gonadotropin regulation




Pituitary gland
FSH β-subunit
LH β-subunit
Inhibin B
FSH
LH
Testosterone
Testis

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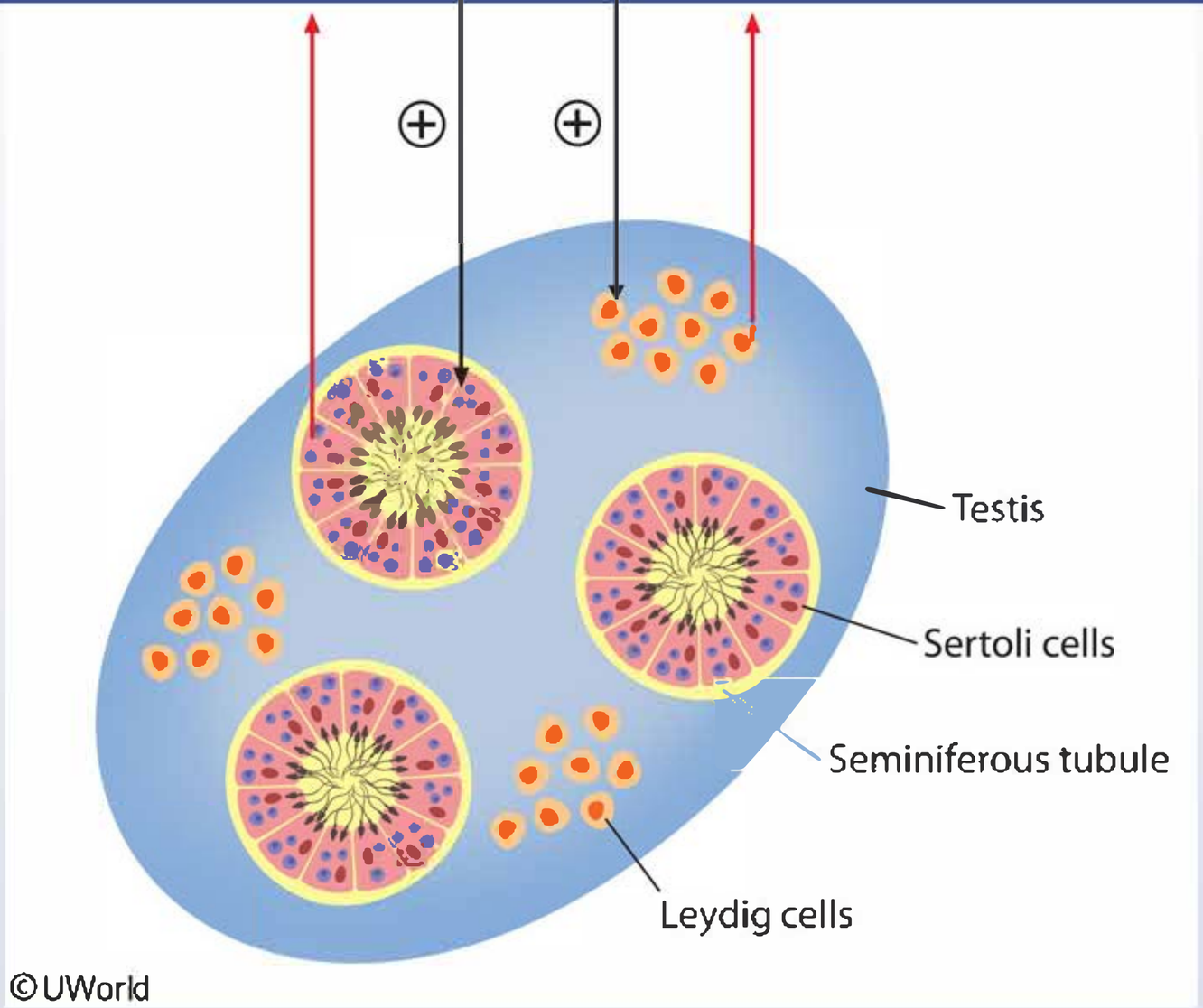

Pulsatile secretion of gonadotrophin-releasing hormone from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and

Pulsatile secretion of gonadotrophin-releasing hormone from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the gonadotroph cells in the anterior pituitary. LH stimulates the release of testosterone from the Leydig cells in the interstitium of the testicles, and FSH stimulates the release of inhibin B from the Sertoli cells in the seminiferous tubules of the testicles. Testosterone and inhibin B induce negative feedback on LH and FSH production, respectively.

FSH also stimulates the Sertoli cells to produce androgen-binding protein locally, within the seminiferous tubules. This androgen-binding protein is responsible for the high local testosterone concentration and is different from sex hormone-binding globulin, which is found in the blood. High local levels of testosterone and FSH are necessary for spermatogenesis. Defective FSH receptors will prevent spermatogenesis and cause low inhibin B levels, because FSH is responsible for both spermatogenesis and inhibin B production.

(Choice A) FSH levels will be high in patients with FSH receptor defects because there is no negative feedback from inhibin B; inhibin B cannot be produced without proper functioning of the FSH pathway.

(Choices B and D) LH and testosterone levels are likely to be normal in this patient because FSH does not play a role in either LH or testosterone feedback. Since the FSH receptor defect is isolated, this patient will have normal testosterone and LH levels.

(Choice E) The circulating levels of other androgens such as DHEA, DHEAS, and androstenedione are also not affected by FSH.

Educational objective:
LH stimulates the release of testosterone from the Leydig cells of the testes; FSH stimulates the release of inhibin B from the Sertoli cells in the seminiferous tubules. Testosterone and inhibin B induce negative feedback on LH and FSH production, respectively.

Physiology	Endocrine, Diabetes & Metabolism	Infertility
Subject	System	Topic

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Biologists investigating the morphologic changes associated with reversible cellular injury perform a procedure on anesthetized mice to assess the effects of transient hepatic ischemia. During the experiment, they clamp the hepatic artery and obtain liver biopsy samples at varying intervals. The samples are then examined by electron microscopy. Cells that are exposed to longer ischemic periods are found to have reduced numbers of ribosomes attached to the endoplasmic reticulum. This structural change is most likely to impair which of the following cellular functions?

A. ATP production

B. Drug detoxification

C. Synthesis of cell membrane proteins

D. Synthesis of cytosolic proteins

E. Synthesis of steroid hormones

Submit

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A. ATP production (3%)

B. Drug detoxification (3%)

✓ C. Synthesis of cell membrane proteins (64%)

D. Synthesis of cytosolic proteins (24%)

E. Synthesis of steroid hormones (4%)

Omitted
Correct answer
C

64%
Answered correctly

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Last Updated

Explanation

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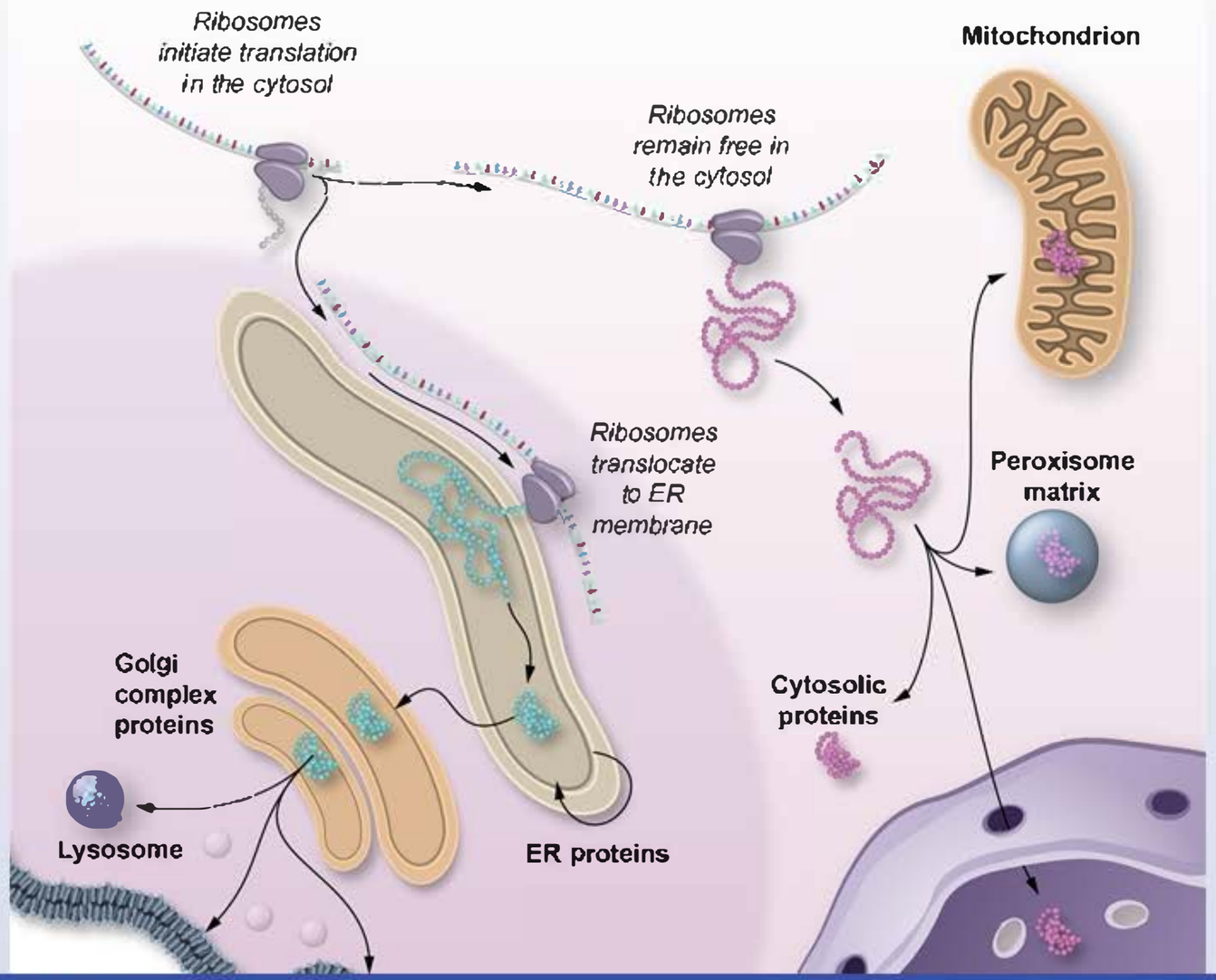
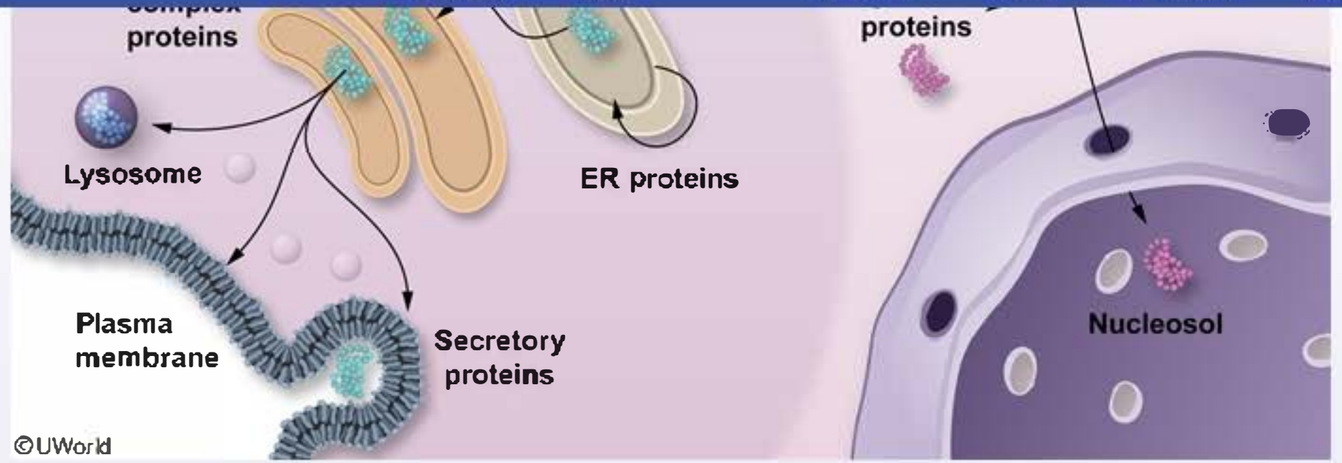
Protein targeting





Ribosomes are cellular organelles that synthesize proteins. Each ribosome consists of 2 subunits. The small ribosomal 40S subunit is responsible for binding mRNA (the protein synthesis template) and tRNA (carries amino acids). The larger 60S subunit contains peptidyl transferase, the enzyme that catalyzes peptide bond formation between amino acids. All ribosomes begin protein translation in the cytoplasm, but some translocate to the rough endoplasmic reticulum (RER) during protein synthesis depending on the protein's target destination.

- **Free ribosomes** remain floating in the cytosol throughout protein synthesis. They are responsible for translating proteins found within the cytosol, nucleosol, peroxisome matrix, and nuclear-encoded mitochondrial proteins (**Choice D**).
- **Attached ribosomes** bind to the RER after protein translation begins. They synthesize most secretory proteins, the integral membrane proteins of the nucleus and cell membrane, and proteins within the ER, Golgi network, and lysosomes.

The RER is particularly well developed in protein-secreting cells (eg, pancreatic and plasma cells). Ribosomes attach to the RER via the **translocon**, a protein complex containing ribophorins that bind the large 60S subunit.

(Choice A) ATP is produced in the cytosol during glycolysis and in the mitochondria during oxidative phosphorylation. The proteins in both of these cellular compartments are synthesized by free ribosomes in the cytosol.

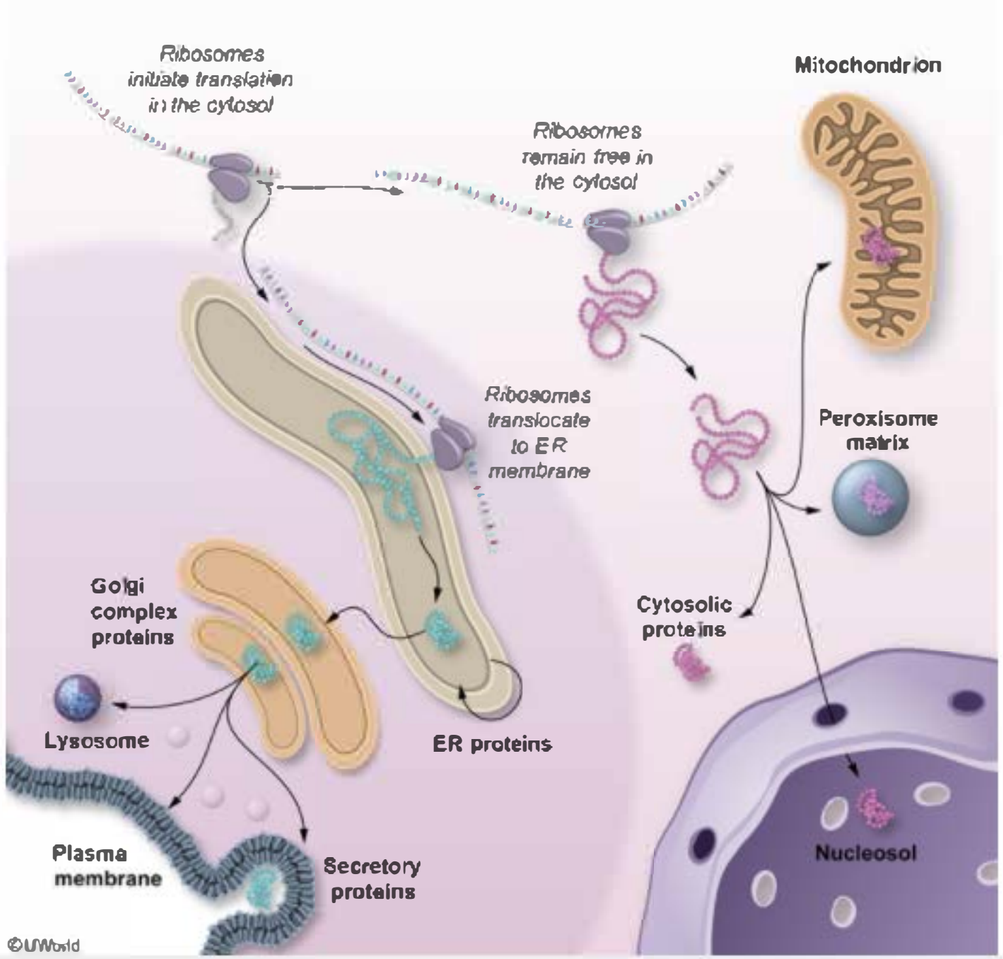
(Choices B and E) Steroid hormone synthesis and drug detoxification are performed by various proteins found within the smooth ER (SER). The SER does not bind to ribosomes as it lacks the translocon complex.

proteins

proteins

Exhibit Display

Protein targeting



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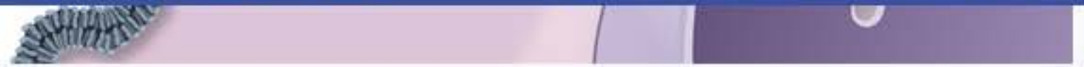

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(Choices B and E) Steroid hormone synthesis and drug detoxification are performed by various proteins found within the smooth ER (SER). The SER does not bind to ribosomes as it lacks the translocon complex.

Educational objective:
The rough endoplasmic reticulum (RER) is covered with ribosomes and is involved in the transfer of proteins to the cell membrane and extracellular space. The RER is well developed in protein-secreting cells. The smooth ER lacks surface ribosomes and functions in lipid synthesis, carbohydrate metabolism, and detoxification of harmful substances.

Physiology	General Principles	Protein synthesis
Subject	System	Topic

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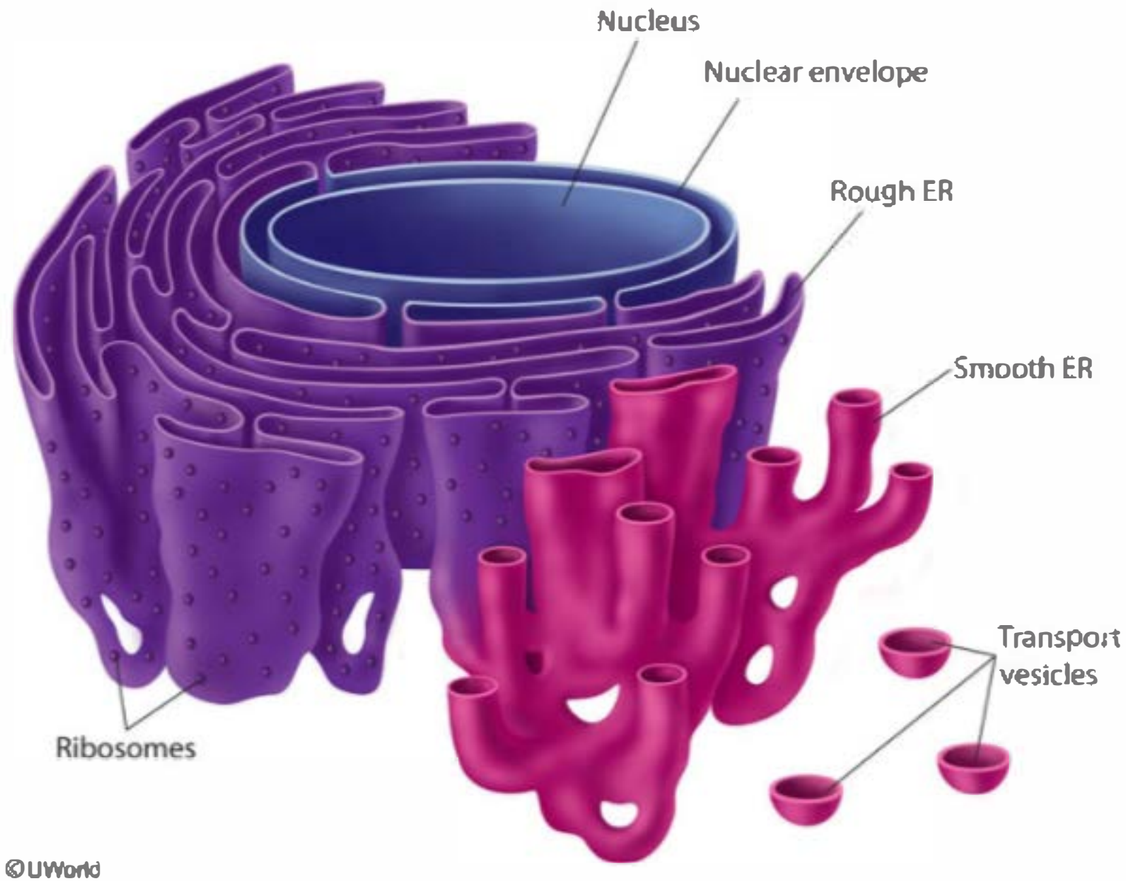
Exhibit Display

Rough & smooth endoplasmic reticulum



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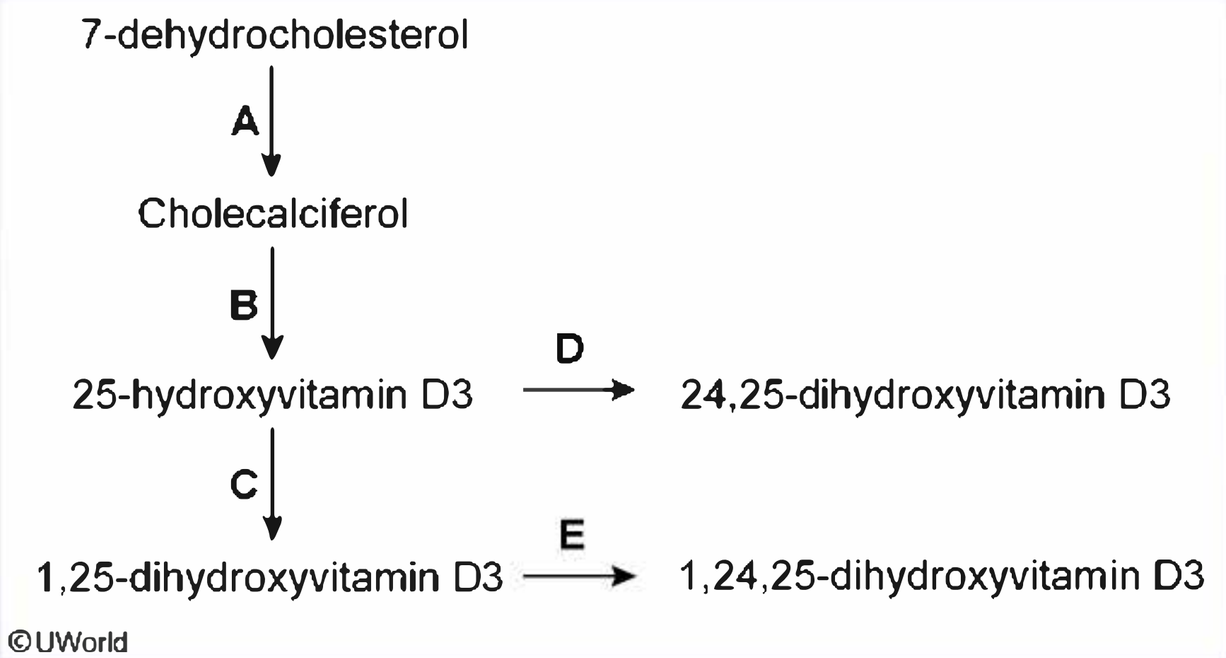
A 34-yearold man with type 1 diabetes mellitus comes to the office due to achy pain in the shoulders, elbows, and thighs over the past several months. The patient was diagnosed with diabetes 15 years ago and has had difficulty adequately controlling it. He currently takes multiple daily injections of insulin. Vital signs are within normal limits. Physical examination shows mild pedal edema. Serum creatinine is 2.2 mg/dL, up from 1.6 mg/dL six months ago. Additional laboratory results show low serum calcium and elevated parathyroid hormone levels. Inhibition of which of the following enzymatic steps is most likely responsible for this patient's current symptoms?



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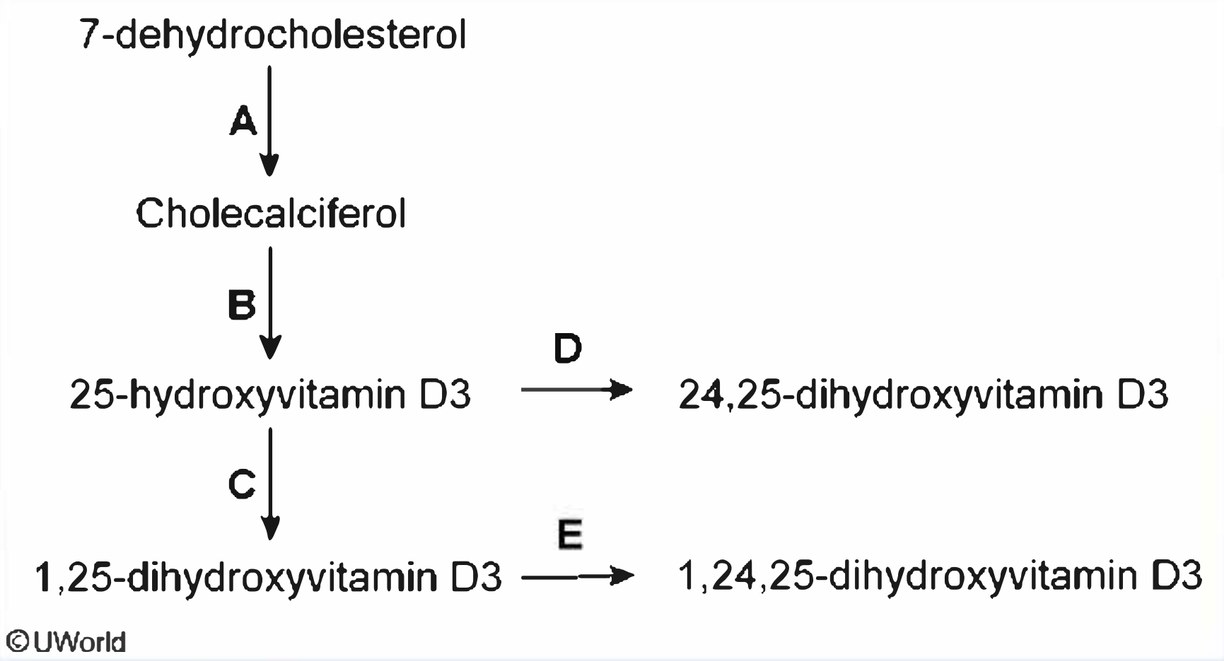

A. A (1%)
B. B (5%)
C. C (82%)
D. D (3%)
E. E (6%)

Omitted
Correct answer

82%
Answered correctly

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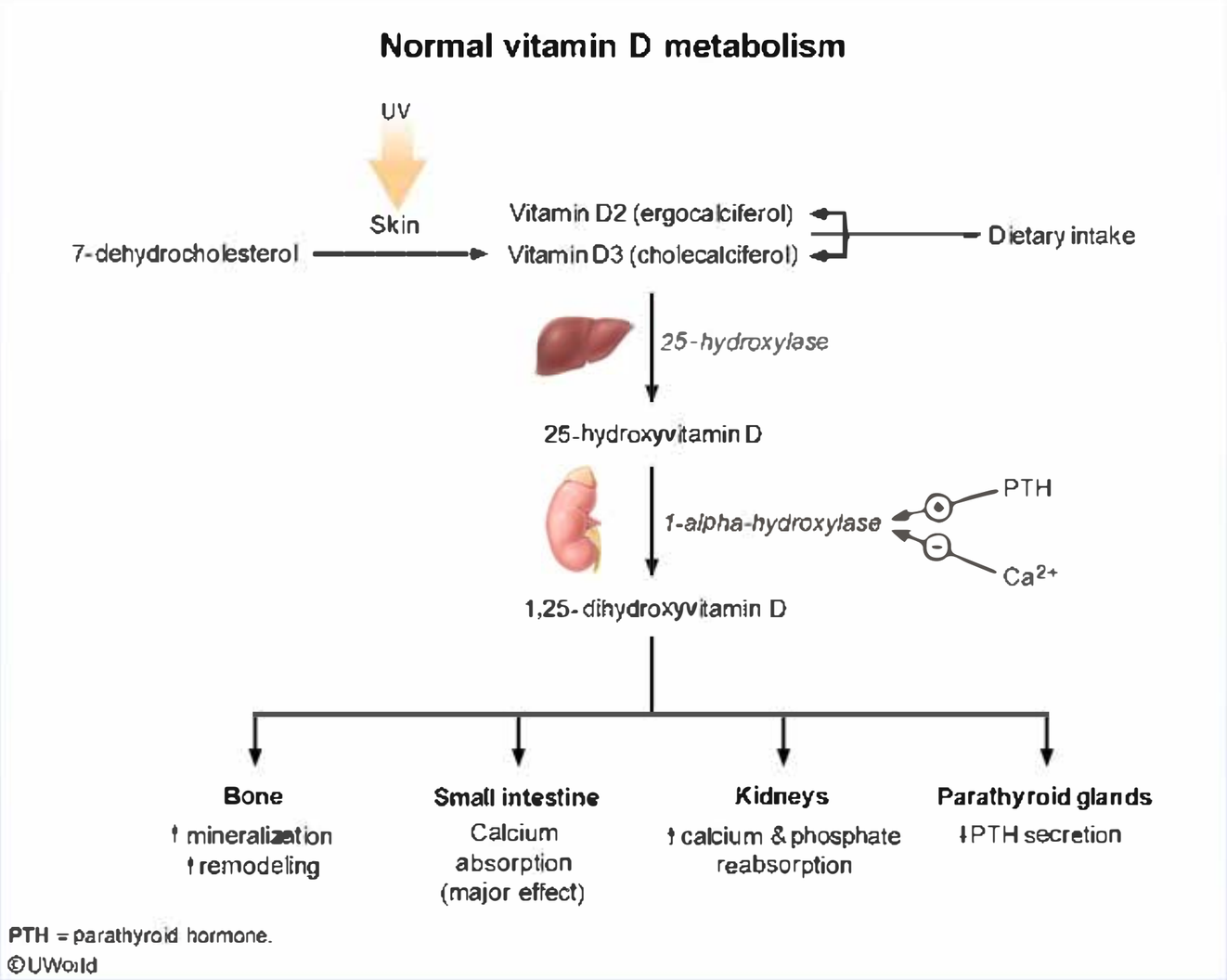

Synthesis of vitamin D begins in the skin with the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3) by ultraviolet light. Cholecalciferol is subsequently converted to 25-hydroxyvitamin D (the primary body store of vitamin D) by 25-hydroxylase in the liver. Finally, **25-**

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Chronic kidney disease (CKD) results in impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D due to the following factors:

- FGF23 levels increase early in CKD, causing direct inhibition of 1-alpha-hydroxylase
- Reduced glomerular filtration limits the delivery of 25-hydroxyvitamin D to proximal tubule cells
- Reduced functional renal mass limits production of 1-alpha-hydroxylase

Inadequate production of 1,25-dihydroxyvitamin D causes reduced intestinal absorption of calcium. This, along with increased phosphate retention (due to impaired glomerular and tubular function), leads to a compensatory increase in parathyroid hormone secretion (**secondary hyperparathyroidism**). Chronically increased PTH levels have a deleterious effect on bone metabolism (**renal osteodystrophy**), and can cause weakness, bone and muscle pain, defective bone mineralization, and an increased risk of fractures.

(Choice A) The initial step in vitamin D synthesis is driven by ultraviolet exposure in the skin. Factors that can lead to vitamin D deficiency include inadequate sunlight exposure (eg, institutionalized elders, living at extreme latitudes), use of high-grade sunblock, nocturnal occupations, and heavily pigmented skin.

(Choice B) 25-Hydroxyvitamin D deficiency due to inadequate 25-hydroxylase activity can be seen in patients with liver disease, but is uncommon and primarily seen in those with advanced cirrhosis.

(Choices D and E) Vitamin D-24-hydroxylase converts 25- and 1,25-dihydroxyvitamin D into inactive 24-hydroxylated metabolites; it functions to degrade excess levels of vitamin D. Although it is expressed predominantly in the kidneys and may be impaired in chronic kidney disease, loss of this enzyme would lead to higher 1,25-dihydroxyvitamin D levels and so would reduce, rather than worsen, the patient's symptoms.

Educational objective:
In chronic kidney disease, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is impaired. In addition, failure of glomerular and tubular

- Reduced functional renal mass limits production of 1-alpha-hydroxylase

Inadequate production of 1,25-dihydroxyvitamin D causes reduced intestinal absorption of calcium. This, along with increased phosphate retention (due to impaired glomerular and tubular function), leads to a compensatory increase in parathyroid hormone secretion (**secondary hyperparathyroidism**). Chronically increased PTH levels have a deleterious effect on bone metabolism (**renal osteodystrophy**), and can cause weakness, bone and muscle pain, defective bone mineralization, and an increased risk of fractures.

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Educational objective:
In chronic kidney disease, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is impaired. In addition, failure of glomerular and tubular function results in phosphate retention and hypocalcemia. This leads to a compensatory rise in parathyroid hormone (secondary hyperparathyroidism) that can present with weakness, muscle and joint pain, defective bone mineralization, and increased fracture risk.

References

- Impaired vitamin D metabolism in CKD.

Physiology	Endocrine, Diabetes & Metabolism	Vitamin D deficiency
Subject	System	Topic

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Biochemists working for a national endocrinology institute are investigating the specifics underlying glucose transport across adipose cell membranes. One of their experiments shows that, in the presence of insulin, D-glucose transport across the plasma membrane of adipocytes is much faster than L-glucose transport. Which of the following transport processes best describes the mechanism for glucose entry into these cells?

A. Simple diffusion

B. Receptor-mediated endocytosis

C. Carrier-mediated transport

D. Primary active transport

E. Co-transport

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A. Simple diffusion (4%)

B. Receptor-mediated endocytosis (16%)

✓ C. Carrier-mediated transport (60%)

D. Primary active transport (7%)

E. Co-transport (10%)

Omitted
Correct answer
C

60%
Answered correctly

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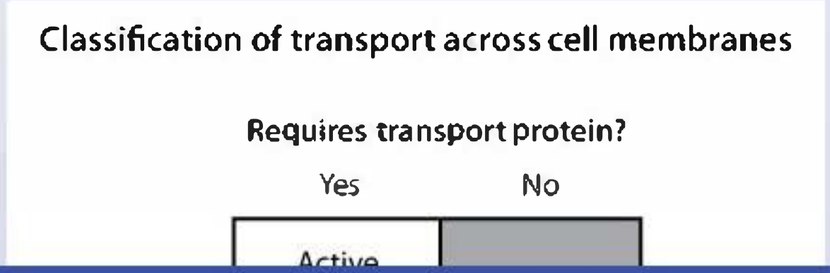
Explanation



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Explanation

Classification of transport across cell membranes

Requires energy?	Requires transport protein? Yes	Requires transport protein? No
Yes	Active transport	
No	Facilitated diffusion	Simple diffusion

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Glucose is the major source of energy for all cells of the body. In the majority of tissues, glucose transport occurs along its concentration gradient, from higher concentrations outside the cell toward lower concentrations inside the cell. However, glucose cannot passively diffuse across the cell membrane in any significant amount and requires carrier proteins to aid its crossing. Transport across the cell membrane by carrier proteins (which undergo conformational changes as the substrate is transported, unlike channel proteins) is termed carrier-mediated transport. Transport that is facilitated by transmembrane proteins without the expenditure of energy is called **facilitated diffusion**.

Transmembrane carrier proteins that belong to the GLUT family transport glucose by facilitated diffusion. These proteins are stereoselective and preferentially catalyze the entrance of D-glucose rather than L-glucose into cells. **GLUT4** is the insulinsensitive transporter found in skeletal muscle cells and adipocytes. In these cells, the GLUT4 protein is stored in cytoplasmic vesicles. Under the influence of insulin, the transporter protein is incorporated into the cell membrane. An increased number of transporters in the membrane leads to an increased rate of glucose uptake by the cells. Another important glucose transporter is **GLUT2**. It facilitates export of glucose from the liver, small intestine, and kidneys into the circulation and also helps to control insulin secretion in the pancreas.

Glucose is the major source of energy for all cells of the body. In the majority of tissues, glucose transport occurs along its concentration gradient, from higher concentrations outside the cell toward lower concentrations inside the cell. However, glucose cannot passively diffuse across the cell membrane in any significant amount and requires carrier proteins to aid its crossing. Transport across the cell membrane by carrier proteins (which undergo conformational changes as the substrate is transported, unlike channel proteins) is termed carrier-mediated transport. Transport that is facilitated by transmembrane proteins without the expenditure of energy is called **facilitated diffusion**.

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(Choice A) Simple diffusion refers to the movement of particles along their concentration gradient directly through the cell membrane. Transport of gases (O_2 and CO_2) occurs via simple diffusion, as the membrane is very permeable to small, nonpolar molecules.

(Choice B) Endocytosis allows for cellular uptake through the formation of membrane-bound, typically clathrin-coated, vesicles. Uptake of cholesterol by cells occurs by means of receptor-mediated endocytosis (mediated by the LDL receptor).

(Choices D and E) Active transport refers to the movement of a substance against its concentration gradient. This process requires energy as well as transport proteins. In primary active transport, the energy required for transport against the concentration gradient is provided by the hydrolysis of ATP. In secondary active transport, this energy is generated by co-transport of a separate substance down its concentration gradient. Transport of glucose against the concentration gradient occurs via the Na/glucose symporter, which is found in the intestinal and renal tubular epithelium and is used to transfer glucose intracellularly from the lumen.

Educational objective:
Transport of glucose into the cells of most tissues occurs by means of facilitated diffusion. Glucose moves from areas of high concentration to areas of low concentration with the help of transmembrane glucose transporter proteins (GLUT). These carrier proteins are stereoselective and have preference for D-glucose.

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Physiology	Endocrine, Diabetes & Metabolism	Cellular transports
Subject	System	Topic

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A 32-year-old woman comes to the office due to neck swelling. The patient says her neck has gradually gotten larger, and she does not like how it appears in the mirror. She otherwise feels well and has no hoarseness, trouble swallowing, or shortness of breath. There is no history of head and neck irradiation. The patient has no prior medical conditions and takes no medications. She has a sister with vitiligo. Blood pressure is 110/60 mm Hg and pulse is 75/min. On physical examination, the thyroid is diffusely enlarged with no palpable nodules. There is no tracheal deviation. Serum TSH and free thyroxine levels are normal. Antibodies against thyroid peroxidase are present in high titers. The antigenic target of these antibodies is involved in which of the following processes?

A. Iodide uptake

B. Iodotyrosine deiodination

C. Thyroglobulin iodination

D. Thyroglobulin synthesis

E. Thyroxine to triiodothyronine conversion

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A. Iodide uptake (4%)

B. Iodotyrosine deiodination (5%)

✓ C. Thyroglobulin iodination (69%)

D. Thyroglobulin synthesis (8%)

E. Thyroxine to triiodothyronine conversion (11%)

Omitted
Correct answer
C

69%
Answered correctly

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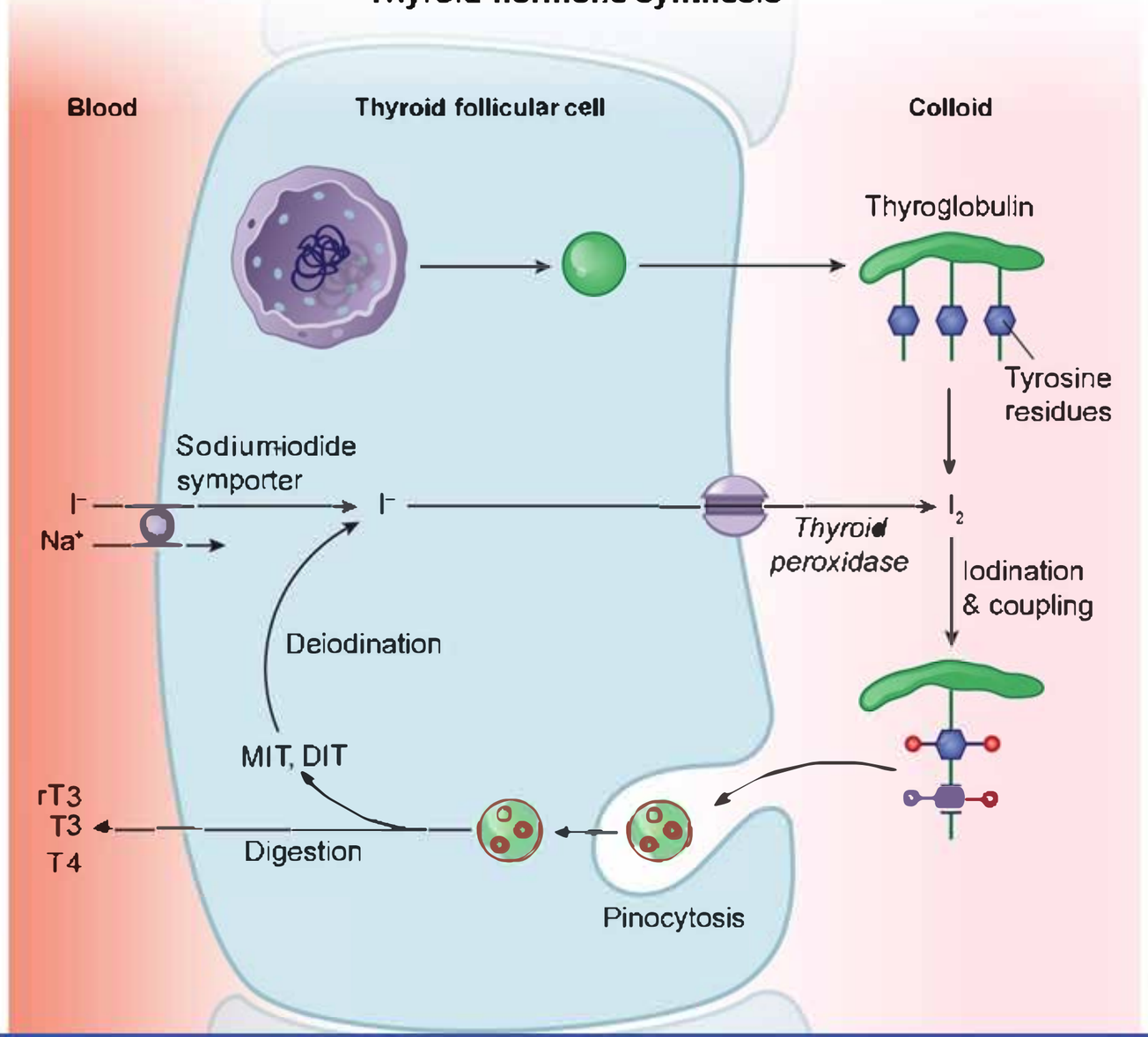
Thyroid hormone synthesis



T4 = thyroxine; **MIT** = monoiodotyrosine.

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Thyroid follicular cells take up iodide (I^-), which is then transported into the thyroid follicular lumen, where it is oxidized to iodine (I_2). Following oxidation, in a process referred to as organification, iodine reacts with tyrosine residues in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) (iodination). While still attached to thyroglobulin, DIT and MIT participate in 2 coupling reactions: The coupling of 2 DITs results in formation of **thyroxine** (T4); the combination of 1 DIT and 1 MIT leads to the formation of **triiodothyronine** (T3). Subsequently, thyroglobulin, which is now attached to multiple iodinated tyrosine compounds (ie, MIT, DIT, T3, T4), is engulfed by the thyroid follicular cells and digested within lysosomes, releasing T3 and T4 into the circulation. Free DIT and MIT are also produced, but only small amounts are secreted because iodotyrosine deiodinase removes the iodine groups from MIT and DIT for recycling **(Choice B)**.

Thyroid peroxidase (TPO) is a multifunctional enzyme that catalyzes the oxidation of iodide, the iodination of thyroglobulin, and the coupling reaction between 2 iodized tyrosine residues. Antibodies against TPO can be seen in a variety of autoimmune thyroid disorders, most commonly chronic lymphocytic (Hashimoto) thyroiditis (90% of patients). Hashimoto thyroiditis is a common cause of diffuse goiter, as in this patient. Although most patients develop residual hypothyroidism (low T4, elevated TSH), early in the disease they may be euthyroid (normal T4, normal TSH) or briefly hyperthyroid (elevated T4, suppressed TSH).

(Choice A) Uptake of iodide from the blood against its concentration gradient is an energy-dependent process carried out by the sodium-iodide symporter and stimulated by TSH. TPO is not involved in iodide uptake.

(Choice D) Thyroglobulin is a high-molecular-weight, glycosylated protein that is the major component of colloid in the thyroid follicle. TPO is involved in iodination, but not synthesis of thyroglobulin.

(Choice E) As noted above, the thyroid produces both T3 and T4, although most is in the form of T4. T3, the more active form of thyroid hormone, is produced primarily in peripheral tissues by deiodination of T4. This reaction is catalyzed by iodothyronine deiodinase, not by TPO.

Educational objective:
Thyroid peroxidase (TPO) catalyzes the oxidation of iodide to iodine, the iodination of thyroglobulin tyrosine residues, and the iodotyrosine coupling reaction that forms T3 and T4. Antibodies against TPO are present in >90% of patients with chronic lymphocytic (Hashimoto) thyroiditis.

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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A 32-year-old woman comes to the office due to a persistent sensation of warmth. For the last 6 months she has felt unusually warm compared to others in the room. The patient has no medical problems and takes no medications or supplements. She does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in her mother. Temperature is 36.7 C (98 F), blood pressure is 130/60 mm Hg, and pulse is 104/min. BMI is 20 kg/m^2. On physical examination, the patient appears anxious and has a staring gaze. There is exophthalmos, lid lag, and a diffusely enlarged thyroid with an audible thyroid bruit. The patient has a fine tremor on outstretched arms, and the skin is warm and moist. Antibodies directed against which of the following are most likely to be found in this patient?

A. Thyroglobulin

B. Thyroid peroxidase

C. Thyrotropin receptor

D. Thyroxine

E. Triiodothyronine

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A 32-year-old woman comes to the office due to a persistent sensation of warmth. For the last 6 months she has felt unusually warm compared to others in the room. The patient has no medical problems and takes no medications or supplements. She does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in her mother. Temperature is 36.7 C (98 F), blood pressure is 130/60 mm Hg, and pulse is 104/min. BMI is 20 kg/m². On physical examination, the patient appears anxious and has a staring gaze. There is exophthalmos, lid lag, and a diffusely enlarged thyroid with an audible thyroid bruit. The patient has a fine tremor on outstretched arms, and the skin is warm and moist. Antibodies directed against which of the following are most likely to be found in this patient?

- A. Thyroglobulin (8%)
- B. Thyroid peroxidase (12%)
- ✓ C. Thyrotropin receptor (77%)
- D. Thyroxine (0%)
- E. Triiodothyronine (0%)

Omitted
Correct answer
C

77%
Answered correctly

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07/04/2020
Last Updated

Explanation

Thyroid autoantibodies	
Antibody	Disease association
	• Graves disease

Thyroid autoantibodies	
Antibody	**Disease association**
Thyrotropin (TSH) receptor antibody	• **Graves disease** • Functional bioassay (thyroid-stimulating immunoglobulin) is also available
Thyroid peroxidase antibody	• **Chronic lymphocytic (Hashimoto) thyroiditis** • Silent thyroiditis • Postpartum thyroiditis • Some patients with Graves disease
Thyroglobulin antibody	• Nonspecific, but more common in hypothyroidism than hyperthyroidism

This patient has signs of hyperthyroidism, including heat intolerance, tachycardia, and lid lag. In light of her diffuse goiter and exophthalmos this is very likely due to **Graves disease**. Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies** (TRAb), which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor antigen is present on other cell types, including fibroblasts and adipocytes. Graves ophthalmopathy is characterized by ocular irritation, impaired extraocular motion, and proptosis; it is caused by T-cell activation and stimulation of orbital fibroblasts by TRAb, leading to expansion of extraocular muscles and retro-orbital tissues.

TRAb binds to extracellular domains on the TSH receptor, a transmembrane G protein–coupled receptor. The G_s alpha subunit activates adenylate cyclase and subsequently the adenylate cyclase second messenger system. Serum TRAb immunoassays have a high sensitivity (97%) and specificity (99%) for Graves disease, although they detect both activating and blocking anti-TSH receptor antibodies. Activating antibodies can be confirmed with a functional bioassay (thyroid-stimulating immunoglobulin) that measures cyclic AMP production by a TSH-receptor–expressing cell line in response to patient serum.

(Choice A) Antibodies to thyroglobulin are thought to reflect disruption of thyroid follicles, which exposes thyroglobulin to the bloodstream. They are present in a number of autoimmune thyroid disorders but are most common in autoimmune hypothyroidism and are present in only a minority of patients with Graves disease.

This patient has signs of hyperthyroidism, including heat intolerance, tachycardia, and lid lag. In light of her diffuse goiter and exophthalmos this is very likely due to **Graves disease**. Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies** (TRAb), which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor antigen is present on other cell types, including fibroblasts and adipocytes. Graves ophthalmopathy is characterized by ocular irritation, impaired extraocular motion, and proptosis; it is caused by T-cell activation and stimulation of orbital fibroblasts by TRAb, leading to expansion of extraocular muscles and retro-orbital tissues.

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(Choice B) Thyroid peroxidase antibodies are most closely associated with Hashimoto thyroiditis and related disorders (eg, silent thyroiditis, postpartum thyroiditis). Hyperthyroidism with exophthalmos is most consistent with Graves disease.

(Choices D and E) Antibodies to thyroxine and triiodothyronine (ie, anti-T4 and anti-T3 immunoglobulins, respectively) can be detected by adding radiolabeled thyroid hormone to the patient's serum followed by precipitation of the antigen-antibody complexes with polyethylene glycol. These antibodies can be seen in a variety of autoimmune thyroid disorders, but are rare.

Educational objective:
Graves disease is an autoimmune disorder triggered by thyrotropin receptor antibodies (TRAb) that bind and activate the TSH receptor. Serum TRAb immunoassays have a high sensitivity and specificity for Graves disease.

References

- Thyrotropin receptor epitope and human leukocyte antigen in Graves disease.

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Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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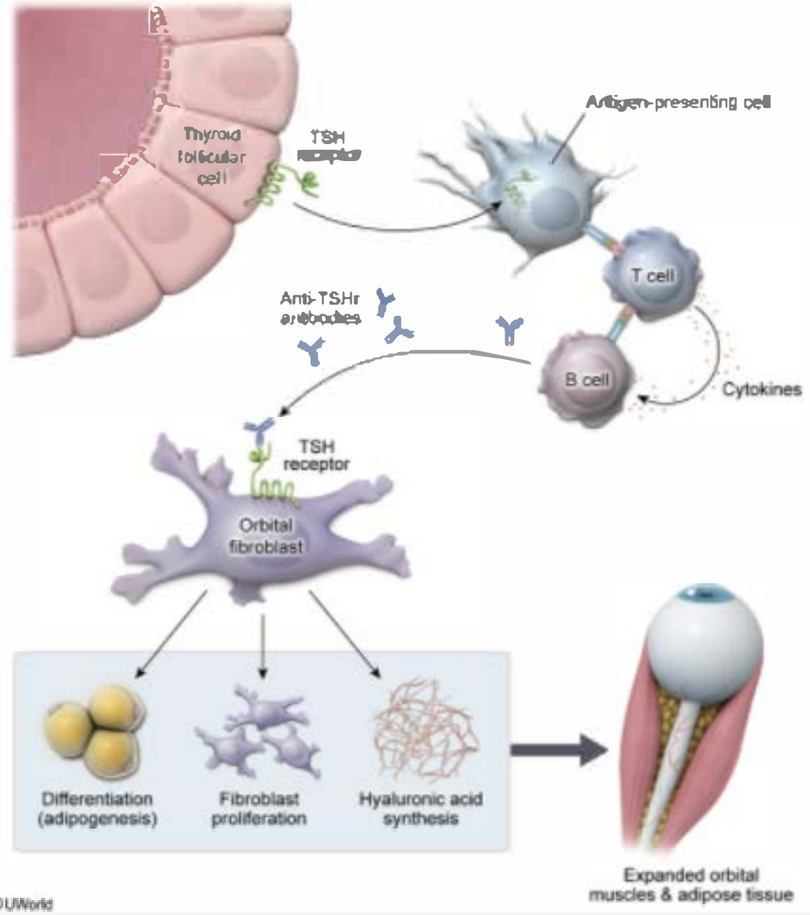
- Functional bioassay (thyroid-stimulating immunoglobulin) is also available

Exhibit Display

Pathogenesis of Graves ophthalmopathy



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Educational objective:

• Functional bioassay (thyroid-stimulating immunoglobulin) is also available

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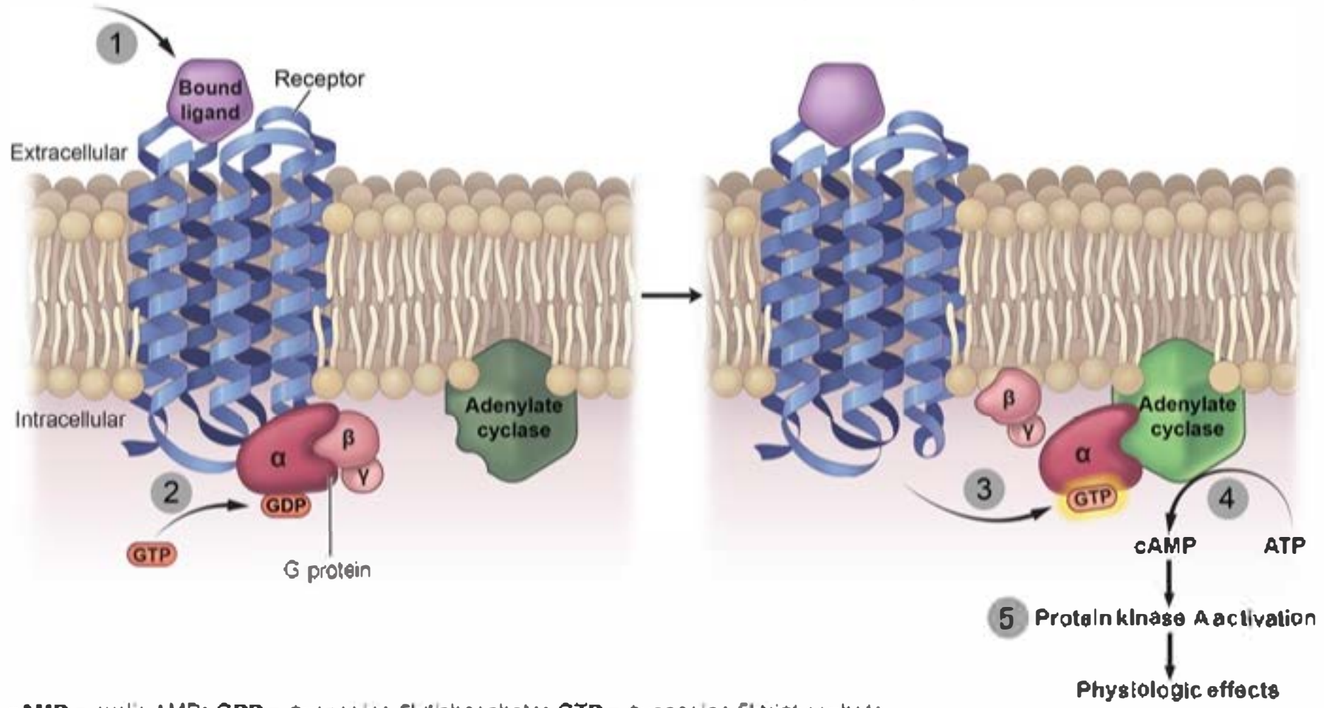
G protein activation of adenylate cyclase



cAMP = cyclic AMP; GDP = guanosine 5'-diphosphate; GTP = guanosine 5'-triphosphate.

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Educational objective:

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Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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A 25-year-old woman is brought to the emergency department due to progressive lethargy. For the last 3 weeks, she has also had loss of appetite, constipation, muscle weakness, and increased thirst and urination. The patient's medical history is unremarkable. She takes no prescription medications but has been taking large doses of vitamin D supplements in the belief that they are beneficial for her health. The patient does not use tobacco, alcohol, or illicit drugs. On physical examination, she is stuporous and has dry mucous membranes. The metabolic abnormality most likely responsible for this patient's clinical findings can also occur in which of the following conditions?

A. Biliary obstruction
B. Carcinoid syndrome
C. Hemochromatosis
D. Pheochromocytoma
E. Sarcoidosis
F. Wilson disease

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- A. Biliary obstruction (5%)
- B. Carcinoid syndrome (12%)
- C. Hemochromatosis (9%)
- D. Pheochromocytoma (6%)
- ✓ E. Sarcoidosis (60%)
- F. Wilson disease (4%)

Omitted
Correct answer
E

60%
Answered correctly

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Explanation

Normal vitamin D metabolism

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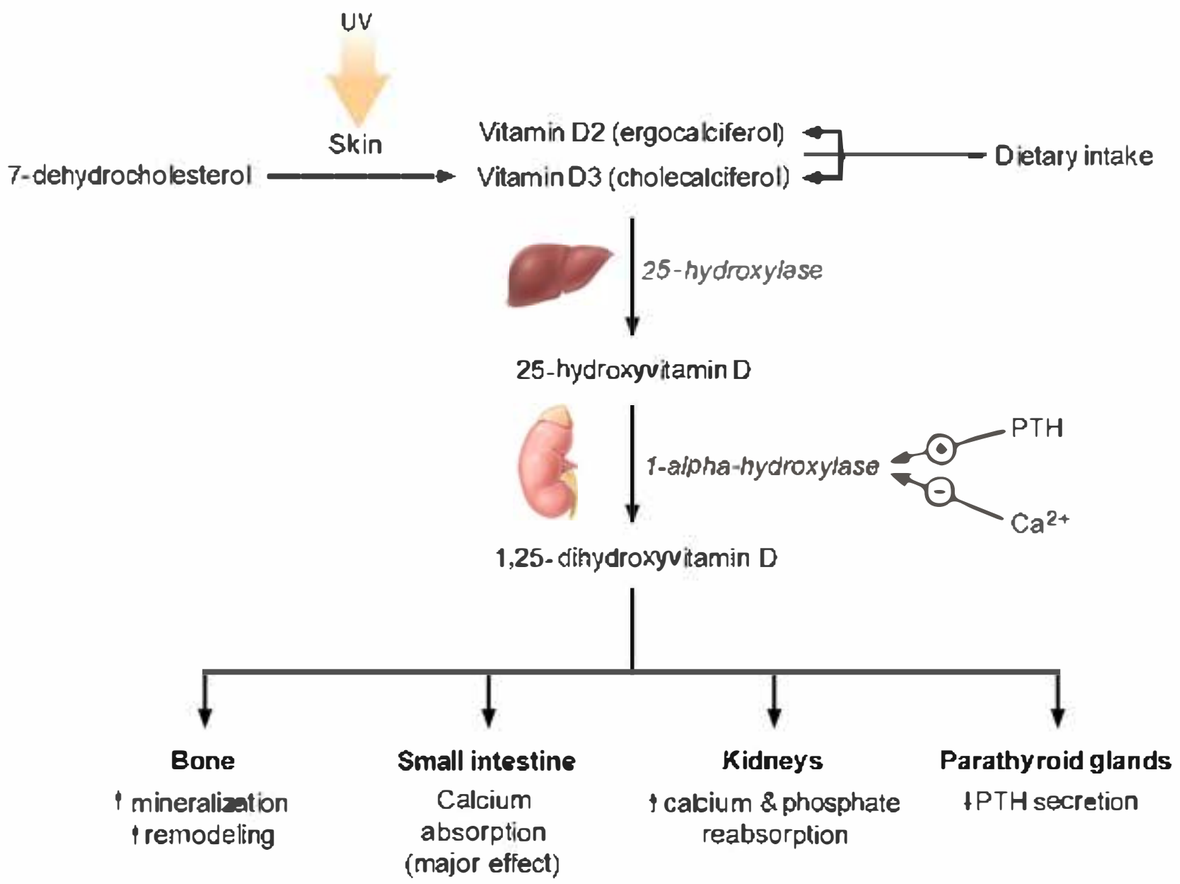
Normal vitamin D metabolism



PTH = parathyroid hormone.
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Moderate doses of vitamin D are often recommended for patients with inadequate dietary intake to improve bone mineralization. However, excessive vitamin D can cause symptomatic **hypercalcemia**, with impaired depolarization of neuromuscular membranes (eg, muscle **weakness**, **constipation**, **confusion**) and impaired concentration of urine in the distal tubule (**polyuria/polydipsia**). Chronic vitamin D intoxication can also

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Moderate doses of vitamin D are often recommended for patients with inadequate dietary intake to improve bone mineralization. However, excessive vitamin D can cause symptomatic **hypercalcemia**, with impaired depolarization of neuromuscular membranes (eg, muscle **weakness**, **constipation**, **confusion**) and impaired concentration of urine in the distal tubule (**polyuria/polydipsia**). Chronic vitamin D intoxication can also lead to **renal stone formation** and bone demineralization with associated **bone pain** (although normal vitamin D levels facilitate bone mineralization; toxicity increases osteoclast activity and bone turnover).

Normally, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D (the active form) by **1-α-hydroxylase** in the kidneys, a process regulated by parathyroid hormone (PTH). However, patients with **granulomatous diseases** (eg, sarcoidosis, tuberculosis) can have **PTH-independent conversion** due to expression of 1-α-hydroxylase in **activated macrophages**. A similar process can occur in Hodgkin disease and some non-Hodgkin lymphomas.

(Choice A) Biliary obstruction is associated with altered lipid absorption and deficiencies of fat-soluble vitamins (eg, A, D, E, and K).

(Choice B) Carcinoid tumor cells synthesize excessive amounts of serotonin. When these cells metastasize to the liver, the release of serotonin into the systemic circulation results in carcinoid syndrome (eg, episodic cutaneous flushing, bronchospasm/wheezing, diarrhea).

(Choice C) Hemochromatosis is associated with excessive intestinal absorption of iron and accumulation in parenchymal organs. Patients classically develop liver cirrhosis, heart failure, skin hyperpigmentation, and diabetes mellitus ("bronze diabetes").

(Choice D) Pheochromocytoma is associated with elevated levels of metanephrines and catecholamines. Patients typically have paroxysmal headache, diaphoresis, tachycardia, and hypertension.

(Choice F) Wilson disease (hepatolenticular degeneration) is characterized by impaired incorporation of copper into ceruloplasmin and defective excretion of excess copper into bile. This leads to elevated blood free copper levels and deposition in the liver (cirrhosis) and brain (motor abnormalities, psychiatric symptoms).

Educational objective:
Excessive vitamin D intake can lead to hypercalcemia and cause mental status changes, muscle weakness, constipation, and polyuria/polydipsia. Activated macrophages in sarcoidosis and other granulomatous diseases express 1-α-hydroxylase, leading to excess production of 1,25-dihydroxyvitamin D and hypercalcemia.

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A 30-yearold woman comes to the office due to excessive weight gain without any changes in her diet or physical activity. She has also been feeling more tired lately and has had frequent constipation. The patient has no prior medical problems and takes no medications. She has been pregnant once and gave birth to a healthy infant 3 years ago. Family history is significant for a thyroid disorder in her mother. Blood pressure is 116/90 mm Hg and pulse is 58/min. BMI is 28.5 kg/m^2. Physical examination reveals a diffusely enlarged and nontender thyroid with no nodules. There is delayed relaxation of deep tendon reflexes. Her hair is thin and the skin appears dry. Which of the following sets of laboratory findings is most likely to be seen in this patient?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)
A.	Increased	Decreased	Normal
B.	Increased	Normal	Normal
C.	Increased	Increased	Increased
D.	Normal	Normal	Decreased
E.	Decreased	Increased	Increased
F.	Decreased	Normal	Normal

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	TSH	Thyroxine (T4)	Triiodothyronine (T3)
✓ A. (83%)	Increased	Decreased	Normal
B. (2%)	Increased	Normal	Normal
C. (1%)	Increased	Increased	Increased
D. (8%)	Normal	Normal	Decreased
E. (2%)	Decreased	Increased	Increased
F. (0%)	Decreased	Normal	Normal

Omitted
Correct answer
A

83%
Answered correctly

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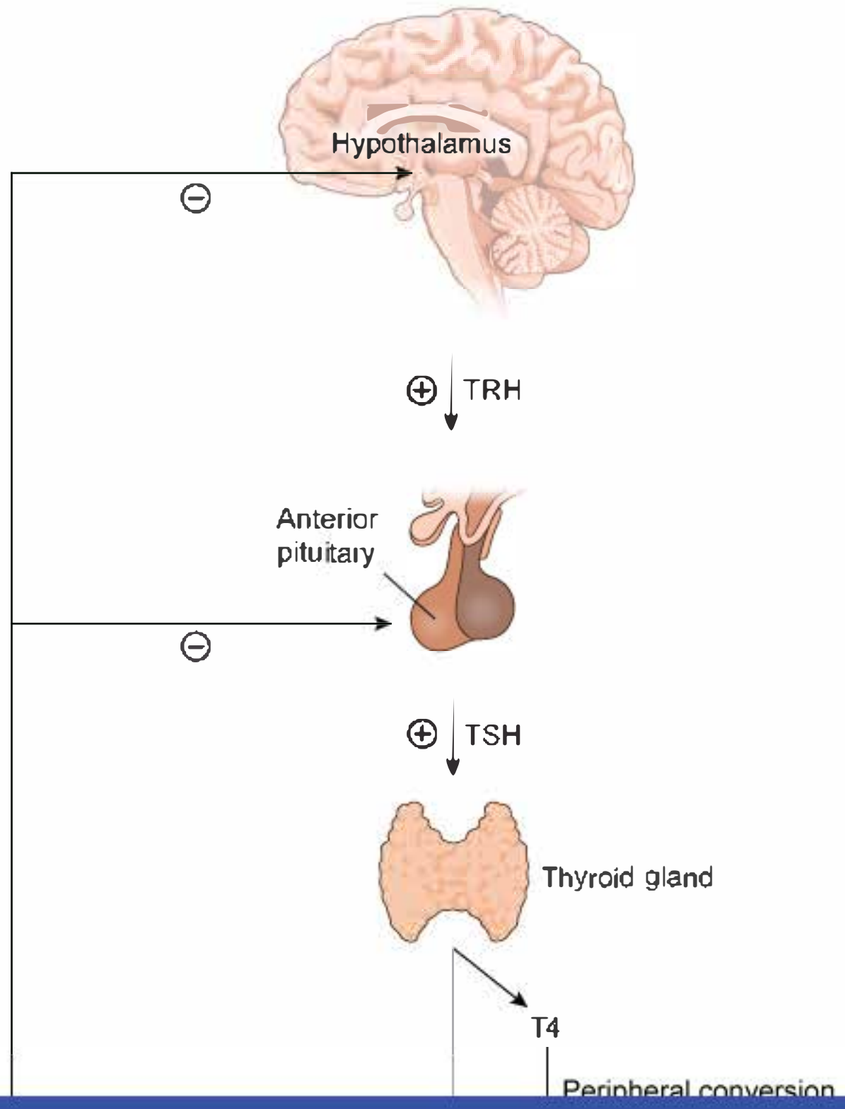
Hypothalamic-pituitary-thyroid axis



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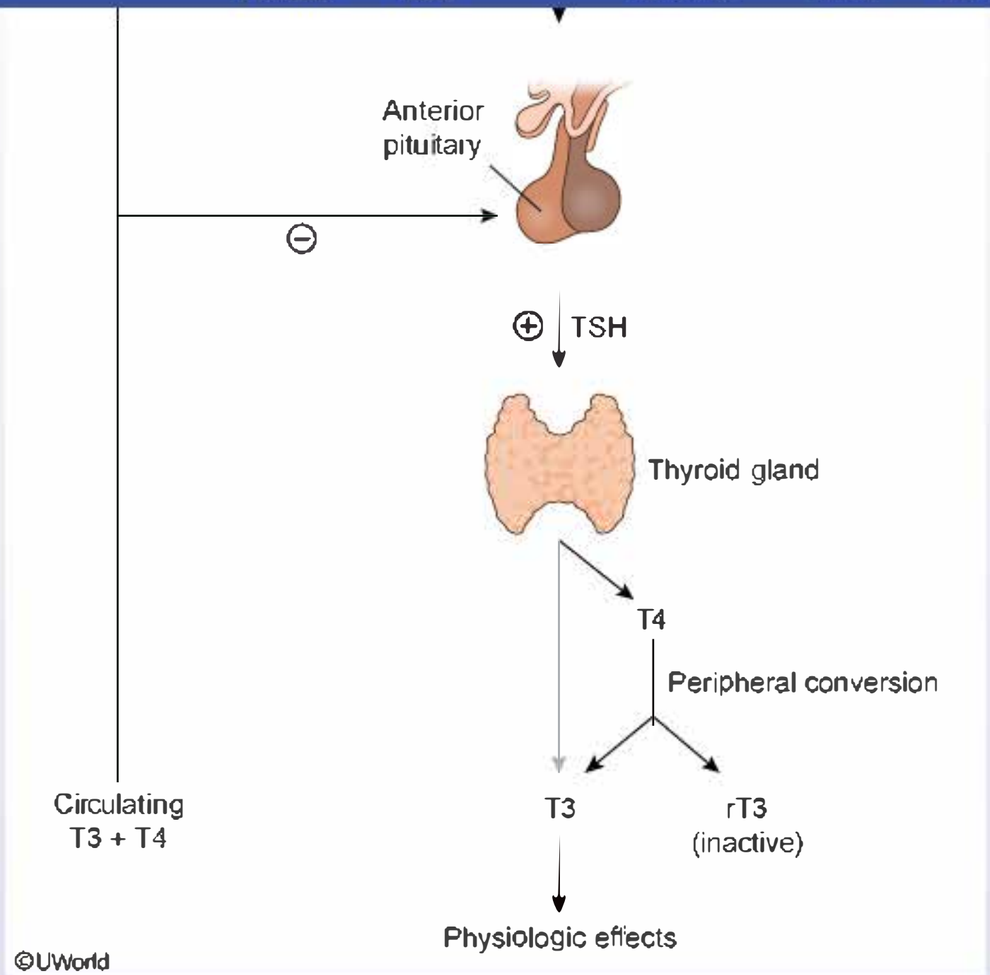

Regulation of thyroid hormone secretion involves feedback inhibition along the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which triggers release of TSH from the pituitary. TSH stimulates secretion of thyroid hormone from the thyroid, which in turn inhibits release of both TRH and TSH. Thyroid hormone exists in 2 primary forms: T4 (thyroxine), the predominant form secreted by the thyroid, and T3 (triiodothyronine), the more active form produced mainly by deiodination of T4 in peripheral tissues.

This patient has a very typical presentation of **primary hypothyroidism** with weight gain, fatigue, and a delayed relaxation phase of deep tendon

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This patient has a very typical presentation of **primary hypothyroidism** with weight gain, fatigue, and a delayed relaxation phase of deep tendon reflexes. Her diffuse goiter suggests chronic autoimmune (Hashimoto) thyroiditis, which is the most common cause of hypothyroidism in developed countries. As autoimmune destruction of the gland progresses, thyroid hormone production declines, leading to loss of feedback inhibition of TSH secretion; therefore, patients have **low T4** and **elevated TSH** levels. However, because T3 is produced mainly in peripheral tissues and has a short half-life, serum T3 levels fluctuate widely and correlate poorly with clinical status; **T3 is often normal** in primary hypothyroidism.

(Choice B) TSH secretion is very sensitive to changes in thyroid status and rises in response to even small declines in thyroid hormone production. Subclinical hypothyroidism is a common biochemical state in which an elevated TSH is necessary to maintain normal thyroid hormone levels. However, most patients are asymptomatic.

(Choices C, E, and F) Primary hyperthyroidism (eg, Graves disease) is characterized by elevated thyroid hormone levels and suppressed TSH. Subclinical hyperthyroidism is characterized by suppressed TSH with normal thyroid hormone levels. Central (secondary) hyperthyroidism (eg, TSH-secreting pituitary adenoma) shows elevated levels of both TSH and thyroid hormone. Common clinical features of hyperthyroidism (primary or secondary) include weight loss, heat intolerance, and tachycardia; patients with subclinical hyperthyroidism may be asymptomatic or have mild symptoms. T3 levels correlate with clinical status in hyperthyroidism more closely than in hypothyroidism and are often elevated.

(Choice D) Euthyroid sick syndrome is a constellation of abnormal thyroid tests seen in patients with severe systemic illness (eg, sepsis). Excess cortisol, inflammatory cytokines, starvation, and certain medications (eg, amiodarone) can cause reduced conversion of T4 to T3, leading to low serum T3; reverse T3 (the inactive metabolite of T4) is typically elevated but TSH and T4 are usually normal.

Educational objective:
Primary hypothyroidism is characterized by decreased T4 levels and increased TSH. T3 is primarily produced by conversion from T4 in peripheral tissues; serum levels widely fluctuate due to its short half life, and can often be within the normal range in patients with hypothyroidism.

References

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References

- Pitfalls in the measurement and interpretation of thyroid function tests

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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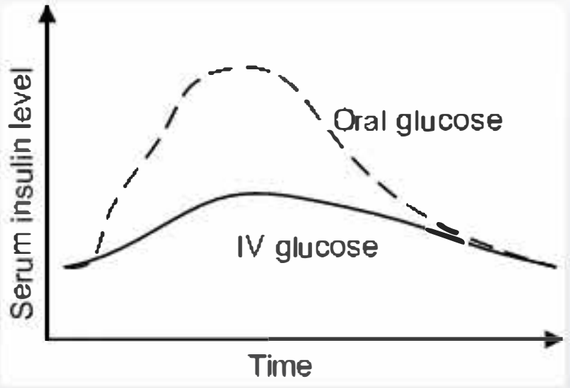
Researchers measure the serum insulin levels of healthy volunteers after equivalent loads of oral and intravenous glucose. The following curves are observed:



Which of the following endogenous substances best explains the difference between the curves?

A. Insulin-like growth factor-1
B. Glucagon-like peptide-1
C. Somatostatin
D. Secretin
E. Cholecystokinin

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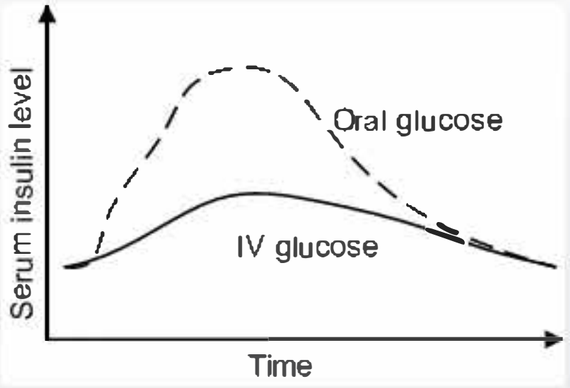

Which of the following endogenous substances best explains the difference between the curves?

A. Insulin-like growth factor-1 (19%)
B. Glucagon-like peptide-1 (51%)
C. Somatostatin (10%)
D. Secretin (12%)
E. Cholecystokinin (6%)

Omitted
Correct answer
B

51%
Answered correctly

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Explanation

Incretins are gastrointestinal hormones produced by the gut mucosa that stimulate pancreatic insulin secretion in response to sugar-containing meals. This response is independent of blood glucose levels, and typically occurs prior to any elevation in blood glucose level following a meal. Two hormones with incretin effects are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Insulin levels will also increase following intravenous administration of glucose due to the sensitivity of the pancreatic beta-cells to increases in blood glucose, but this increase will not be as marked as that seen following oral glucose administration because the effect of incretin is absent.

(Choice A) Insulin-like growth factor-1 is produced by the liver in response to stimulation by growth hormone. It functions as a mitogen and as an inhibitor of apoptosis.

(Choice C) Somatostatin is produced by cells in the stomach, small bowel and pancreas and inhibits the production and release of most other gastrointestinal hormones, including insulin.

(Choice D) Secretin is a hormone produced in the duodenum in response to increased luminal acidity. It stimulates the release of bicarbonate-rich secretions from the pancreas, gallbladder and duodenum. It also increases the activity of cholecystokinin.

(Choice E) Cholecystokinin is produced by the duodenum in response to a fat or protein-rich meal. It has many functions including inhibition of further gastric emptying, stimulation of pancreatic enzyme secretion and stimulation of bile production and gallbladder contraction.

Educational objective:
Incretin functions by stimulating insulin release following oral consumption of glucose. Incretin-stimulated insulin release is independent of the increase in insulin secretion brought on by elevations in the blood glucose level.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 67-year-old man comes to the office due to increased fatigue and weight gain over the past 6 months. He has hypertension controlled with a calcium channel blocker. Two years ago, the patient's physical examination was unremarkable, and his blood tests, including a lipid panel, were normal. Blood pressure is 135/98 mm Hg, and pulse is 62/min. BMI is 28 kg/m^2. On physical examination, the thyroid appears to be mildly enlarged and is irregular and firm in consistency. Laboratory studies reveal elevated TSH, low free thyroxine (T4), high total and LDL cholesterol, and mildly elevated triglyceride levels. Which of the following is the most likely underlying mechanism for the elevated cholesterol in this patient?

- A. Activation of transcription factor peroxisome proliferator–activated receptor alpha
- B. Decreased LDL receptor gene expression
- C. Increased lipoprotein lipase gene expression
- D. Induction of HMG-CoA reductase
- E. Upregulation of LDL receptor degradation

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A. Activation of transcription factor peroxisome proliferator–activated receptor alpha (9%)

✓ B. Decreased LDL receptor gene expression (57%)

C. Increased lipoprotein lipase gene expression (7%)

D. Induction of HMG-CoA reductase (13%)

E. Upregulation of LDL receptor degradation (11%)

Omitted
Correct answer
B

57%
Answered correctly

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01/22/2020
Last Updated

Explanation

Hypothyroidism effect on lipids

Normal thyroid	Hypothyroid
	Hypercholestrolemia

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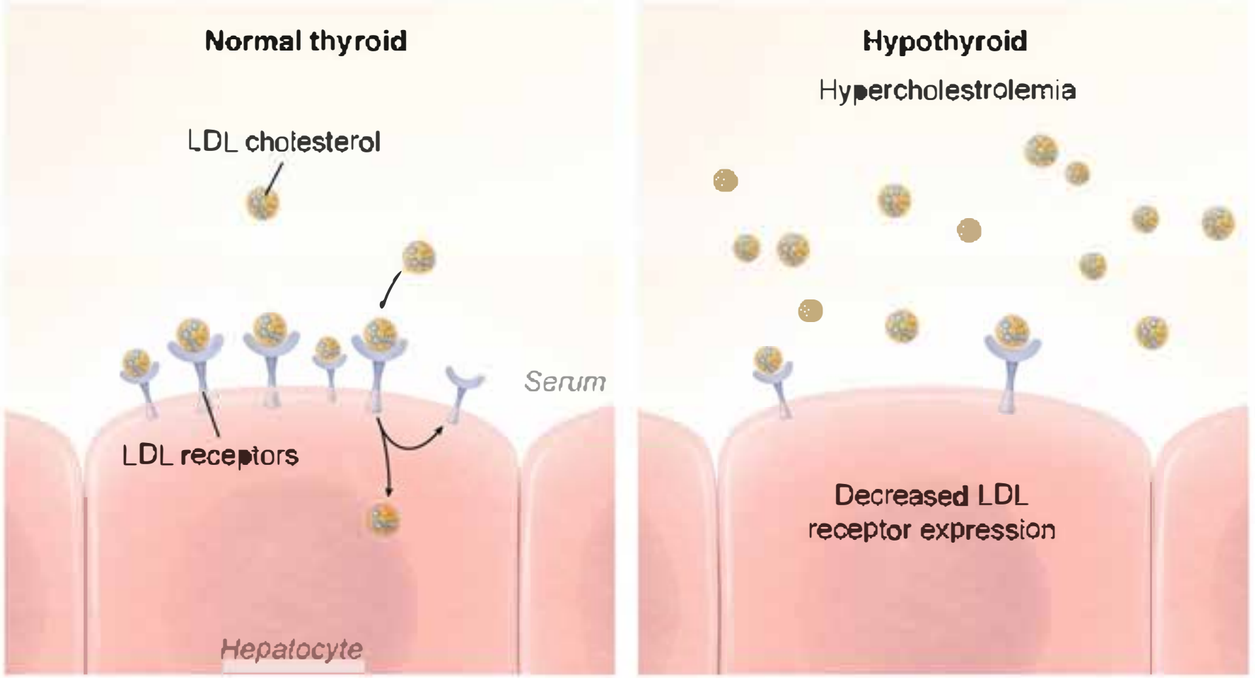
Hypothyroidism effect on lipids



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This patient has primary hypothyroidism presenting with fatigue, weight gain, and goiter, along with elevated TSH and low free thyroxine (T4) levels. **Hypothyroidism** can cause a number of adverse effects on serum lipids, including elevating total cholesterol, LDL cholesterol, and triglyceride levels.

Hypothyroidism causes **decreased LDL receptor expression**, leading to decreased clearance of LDL with resultant **increased blood LDL** levels. Hypothyroidism may also decrease LDL receptor activity and biliary excretion of cholesterol. Hypertriglyceridemia can occur in hypothyroidism due to decreased expression of lipoprotein lipase **(Choice C)**. Along with effects on blood pressure (eg, hypertension due to increased peripheral vascular resistance), the adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

(Choice A) Peroxisome proliferator-activated receptor alpha (PPAR-α) stimulates fatty acid uptake and beta oxidation; increased PPAR-α

This patient has primary hypothyroidism presenting with fatigue, weight gain, and goiter, along with elevated TSH and low free thyroxine (T4) levels. **Hypothyroidism** can cause a number of adverse effects on serum lipids, including elevating total cholesterol, LDL cholesterol, and triglyceride levels.

Hypothyroidism causes **decreased LDL receptor expression**, leading to decreased clearance of LDL with resultant **increased blood LDL** levels. Hypothyroidism may also decrease LDL receptor activity and biliary excretion of cholesterol. Hypertriglyceridemia can occur in hypothyroidism due to decreased expression of lipoprotein lipase **(Choice C)**. Along with effects on blood pressure (eg, hypertension due to increased peripheral vascular resistance), the adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

(Choice A) Peroxisome proliferator–activated receptor alpha (PPAR-α) stimulates fatty-acid uptake and beta oxidation; increased PPAR-α expression would cause a reduction in triglyceride levels. Decreased PPAR-α activity leads to hypertriglyceridemia and lipid accumulation within the liver (fatty liver disease) but is not associated with hypothyroidism.

(Choice D) Hypothyroidism is associated with decreased activity of HMG-CoA reductase and therefore decreased de novo synthesis of cholesterol; however, patients still develop hyperlipidemia due to reduced LDL clearance. Thyroid hormone (not hypothyroidism) induces expression of HMG-CoA reductase.

(Choice E) Similar to decreased LDL receptor expression, increased LDL receptor degradation leads to elevated blood LDL levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases the degradation of hepatic LDL receptors; alirocumab, a monoclonal antibody against PCSK9, blocks this effect, leading to a reduction in LDL levels. However, hypothyroidism is not associated with increased LDL receptor degradation.

Educational objective:
Hypothyroidism causes decreased expression of LDL receptors in the liver, leading to decreased clearance of LDL and increased blood LDL levels. It also causes hypertriglyceridemia due to decreased expression of lipoprotein lipase. The adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

References

- Effects of thyroid dysfunction on lipid profile.

Physiology Endocrine, Diabetes & Metabolism Hypothyroidism

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A 45-year-old man is evaluated for a progressively enlarging neck mass and hoarseness. Physical examination shows an enlarged and nontender left thyroid lobe. Fine-needle aspiration biopsy is positive for papillary thyroid cancer, and a thyroidectomy is subsequently performed. On the second postoperative day, the patient develops tingling around the mouth and muscle cramps in his lower extremities. Blood pressure is 120/80 mm Hg, pulse is 82/min, and respirations are 14/min. Physical examination shows normal muscle strength and deep tendon reflexes. Light tapping anterior to the ear elicits twitching of the lower facial muscles. An increase in which of the following best explains this patient's current symptoms?

A. Calcium binding by albumin
B. Calcium release from bones
C. Hydroxylation of vitamin D
D. Intestinal phosphate absorption
E. Urinary calcium excretion

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A. Calcium binding by albumin (8%)
B. Calcium release from bones (11%)
C. Hydroxylation of vitamin D (2%)
D. Intestinal phosphate absorption (7%)
✓ E. Urinary calcium excretion (70%)

Omitted
Correct answer
E

70%
Answered correctly

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Time Spent

02/29/2020
Last Updated

Explanation

PTH, vitamin D & calcium axis

Negative inhibition → PTH release from

Negative inhibition

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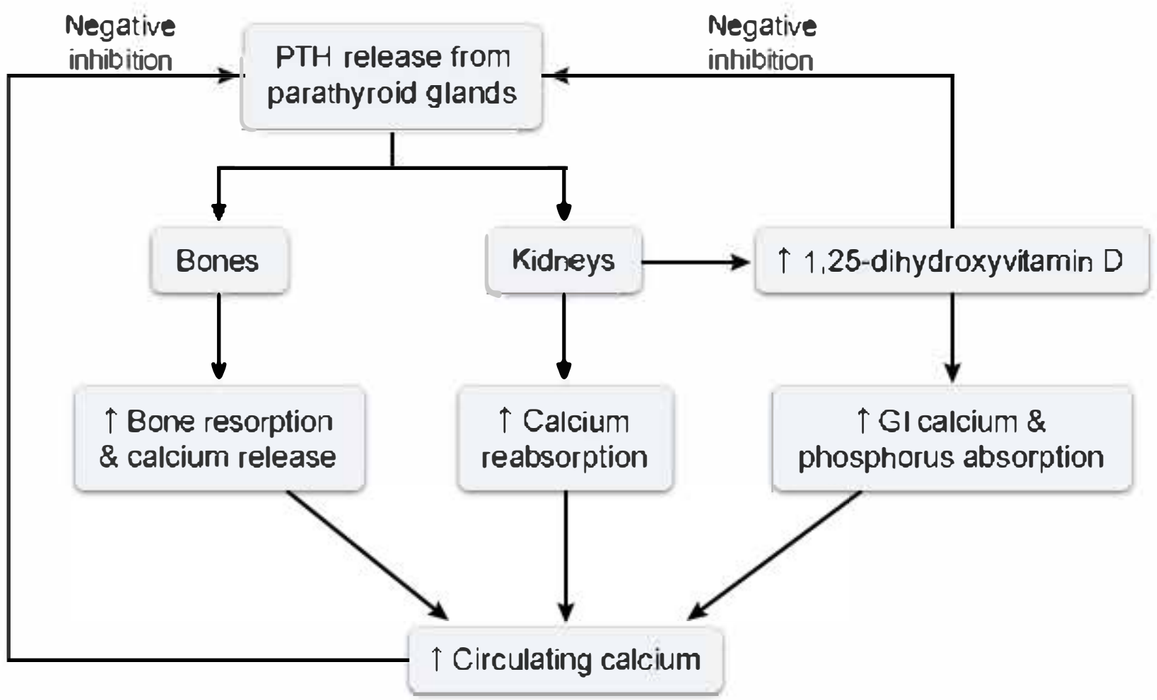
PTH, vitamin D & calcium axis



GI = gastrointestinal; PTH = parathyroid hormone

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This patient has perioral paresthesias and a positive Chvostek sign, which are typical manifestations of acute **hypocalcemia**. Hypocalcemia is a common complication of thyroid surgery due to iatrogenic injury (eg, devascularization, inadvertent removal) to the parathyroid glands and subsequent **hypoparathyroidism**.

Calcium and phosphate homeostasis is regulated by 2 primary hormones: **parathyroid hormone** (PTH), which regulates minute-to-minute concentrations, and **vitamin D**, which regulates levels over the longer term. PTH is a polypeptide hormone that is produced by the chief cells of the parathyroid glands in response to hypocalcemia and has 3 primary effects:

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- Increases osteoclastic **bone resorption**, which releases calcium and phosphate into the circulation
- Increases **renal calcium reabsorption** and reduces phosphate reabsorption
- Increases formation of **1,25-dihydroxyvitamin D** (by upregulating renal 1-alpha-hydroxylase), which increases intestinal calcium absorption

Acute hypoparathyroidism results in decreased calcium and phosphate release from bone **(Choice B)** and **decreased calcium reabsorption** by the kidneys. Inadequate PTH also reduces phosphate excretion by the kidneys and decreases the hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form) in the renal tubular cells **(Choice C)**. This, in turn, decreases intestinal absorption of calcium and phosphate **(Choice D)**.

(Choice A) Elevated plasma pH enhances the binding of calcium to albumin, which leading to a precipitous drop in ionized calcium concentration that can induce symptoms of hypocalcemia. However, this patient has no indication of a respiratory (eg, tachypnea) or metabolic (eg, vomiting, hypovolemia) alkalosis.

Educational objective:
Postoperative hypocalcemia is common after thyroid surgery, due to inadvertent removal or damage to the parathyroid glands. The acute drop in parathyroid hormone level results in decreased calcium and phosphate resorption from bone and decreased calcium reabsorption by the kidneys.

References

- Parathyroid disorders.
- Defining the syndromes of parathyroid failure after total thyroidectomy.

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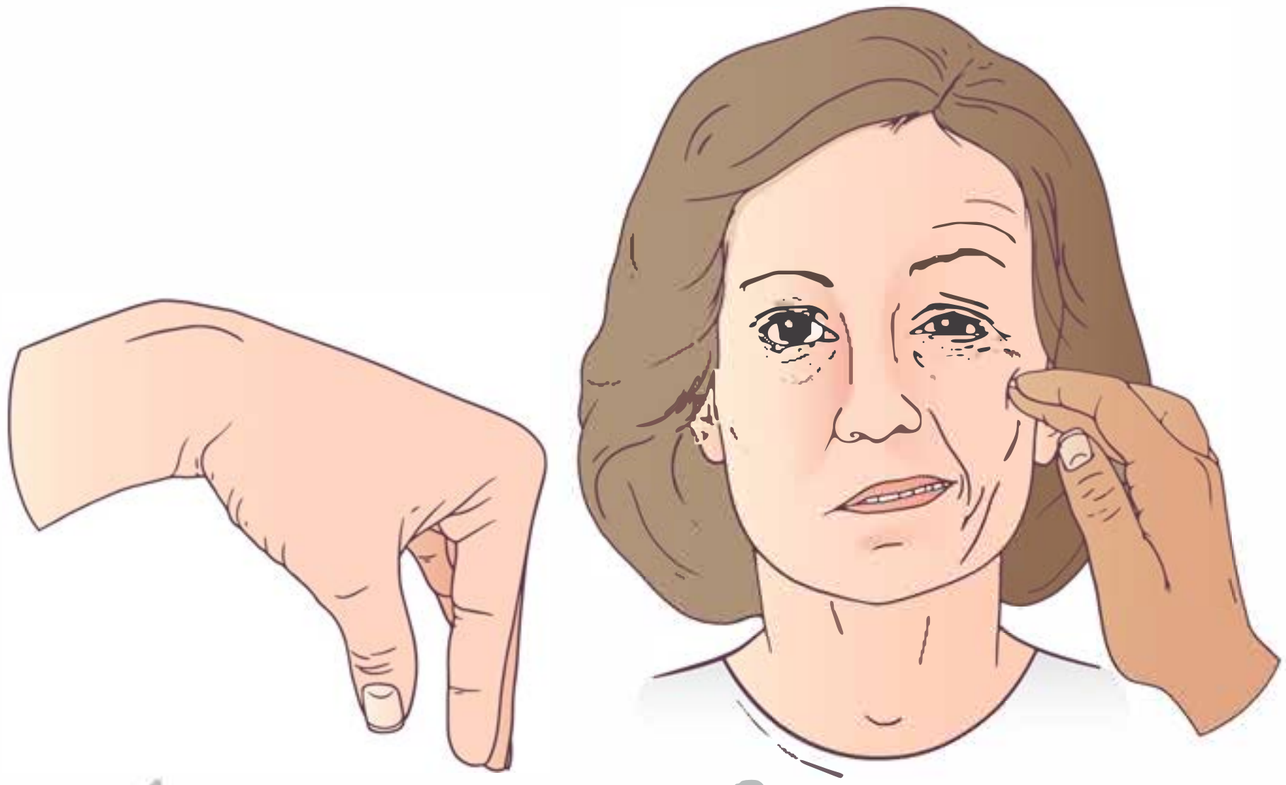
Exhibit Display

Signs of hypocalcemia



1 Trousseau sign

2 Chvostek sign

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A 16-year-old boy is brought to the office for evaluation of irritability, slow growth, and acne. The patient plays soccer and has been following an aggressive strength-training program. When asked, he admits to using a performance-enhancing substance for the past 6 months. What additional findings would most likely be present in this patient now compared to 6 months ago?

	Serum LH	Serum estrogen	Spermatogenesis
A.	High	High	High
B.	High	High	Low
C.	High	Low	Low
D.	Low	High	High
E.	Low	High	Low
F.	Low	Low	Low

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	Serum LH	Serum estrogen	Spermatogenesis
A. (0%)	High	High	High
B. (4%)	High	High	Low
C. (2%)	High	Low	Low
D. (3%)	Low	High	High
✓ E. (73%)	Low	High	Low
F. (15%)	Low	Low	Low

Omitted
Correct answer
E

73%
Answered correctly

02 secs
Time Spent

05/07/2020
Last Updated

Explanation

Clinical features of anabolic steroid abuse	
Musculoskeletal	• ↑ Muscle mass
Endocrine/reproductive	• ↓ FSH, LH; ↑ estradiol • Testicular atrophy • ↓ Spermatogenesis
Hematologic	• Erythrocytosis
Psychological	• Affective symptoms • Aggression
Dermatologic/breast	• Acne • Gynecomastia

Testosterone stimulates increased protein synthesis by skeletal myocytes. Some competitive athletes and body builders **abuse testosterone** and other exogenous androgens to increase muscle mass and improve athletic performance. However, excessive androgenic activity can cause significant adverse effects, including **acne** (increased dermal sebum production) and neuropsychiatric changes (eg, **irritability**, **aggression**, and anxiety).

Androgen abuse can also result in profound endocrine and reproductive effects. Spermatogenesis in the seminiferous tubules is driven by FSH and requires a high local concentration of testosterone, which is produced by nearby Leydig cells and retained by androgen-binding protein. Exogenous androgens suppress GnRH, LH, and FSH secretion, leading to reduced endogenous testosterone secretion, **impaired spermatogenesis (Choice D)**, and **testicular atrophy**.

In addition, excess testosterone is converted by aromatase to yield high levels of estradiol **(Choice F)**, which can lead to **gynecomastia**. In adolescent users, high circulating estrogen levels can also cause **premature epiphyseal closure** and short stature.

(Choices A, B, and C) Excess circulating exogenous androgens (eg, testosterone) suppress pituitary LH release.

Educational objective:

Psychological	• Aggression
Dermatologic/breast	• Acne • Gynecomastia

Testosterone stimulates increased protein synthesis by skeletal myocytes. Some competitive athletes and body builders **abuse testosterone** and other exogenous androgens to increase muscle mass and improve athletic performance. However, excessive androgenic activity can cause significant adverse effects, including **acne** (increased dermal sebum production) and neuropsychiatric changes (eg, **irritability**, **aggression**, and anxiety).

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Educational objective:
Androgen abuse suppresses GnRH, LH, and FSH secretion, leading to reduced endogenous testosterone secretion, impaired spermatogenesis, and testicular atrophy. In addition, excess testosterone is converted by aromatase to estradiol, which can lead to gynecomastia.

References

• Performance-enhancing drug use in adolescence.

Physiology	Endocrine, Diabetes & Metabolism	Infertility
Subject	System	Topic

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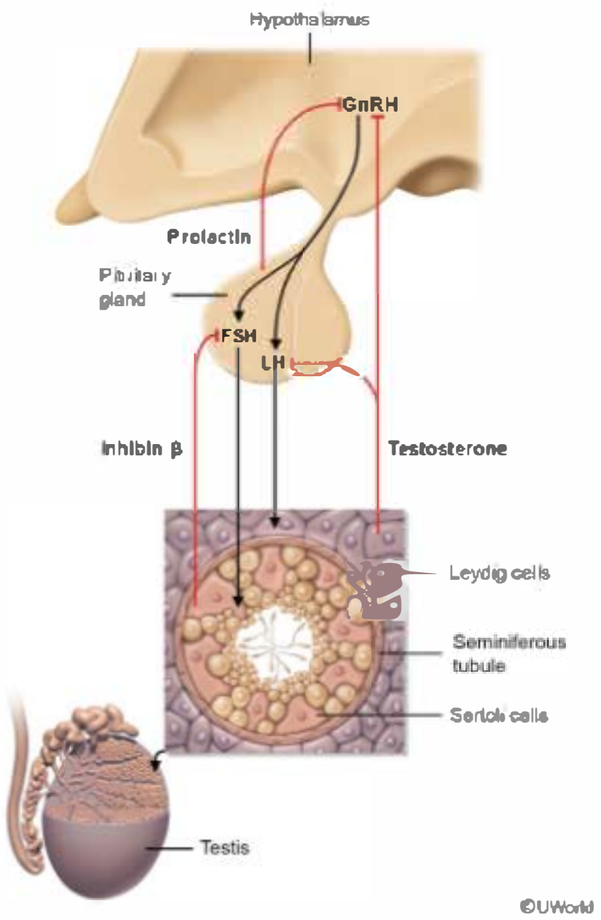
Psychological

- Aggression

Exhibit Display

Prolactin and gonadotropin production



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Fifty obese adults without diabetes mellitus are enrolled in a 10-week weight loss program. The program includes a low-calorie diet and moderate-intensity exercise for at least 150 minutes per week. The study subjects who are adherent to the regimen lose an average of 7 kg (15.5 lb) at the end of 10 weeks. Venous blood samples to study biochemical changes induced by weight loss are taken at the start of the trial and at the 10-week follow-up visit. Which of the following hormonal changes are likely to occur during the course of the study?

	Ghrelin	Leptin	Insulin
A.	↑	↓	↓
B.	↓	↓	↓
C.	↓	↑	↑
D.	↑	↓	↑
E.	↑	↑	↓

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	Ghrelin	Leptin	Insulin
✓ A. (44%)	↑	↓	↓
B. (11%)	↓	↓	↓
C. (28%)	↓	↑	↑
D. (8%)	↑	↓	↑
E. (6%)	↑	↑	↓

Omitted
Correct answer
A

44%
Answered correctly

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Explanation

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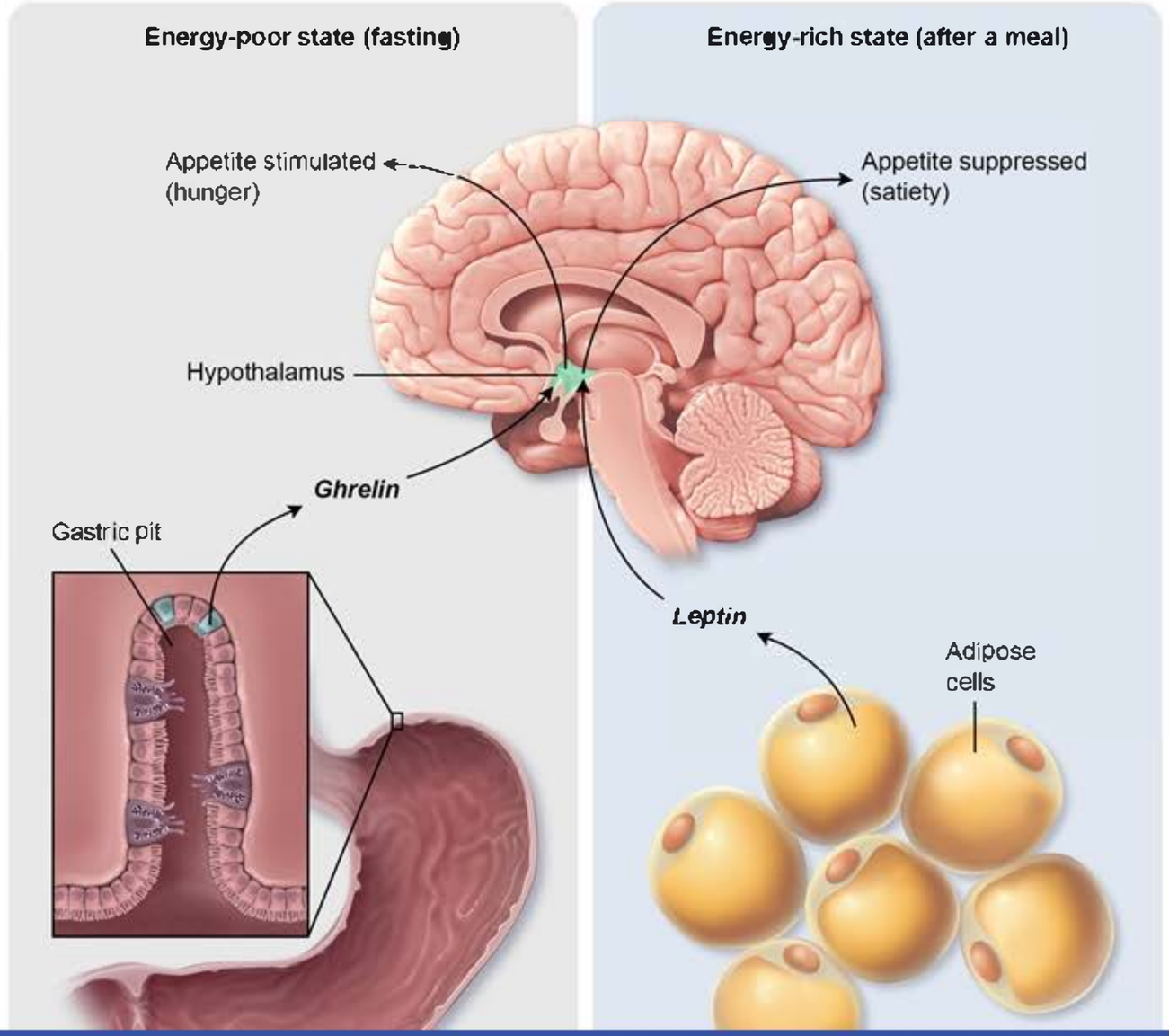
Appetite hormones: leptin & ghrelin



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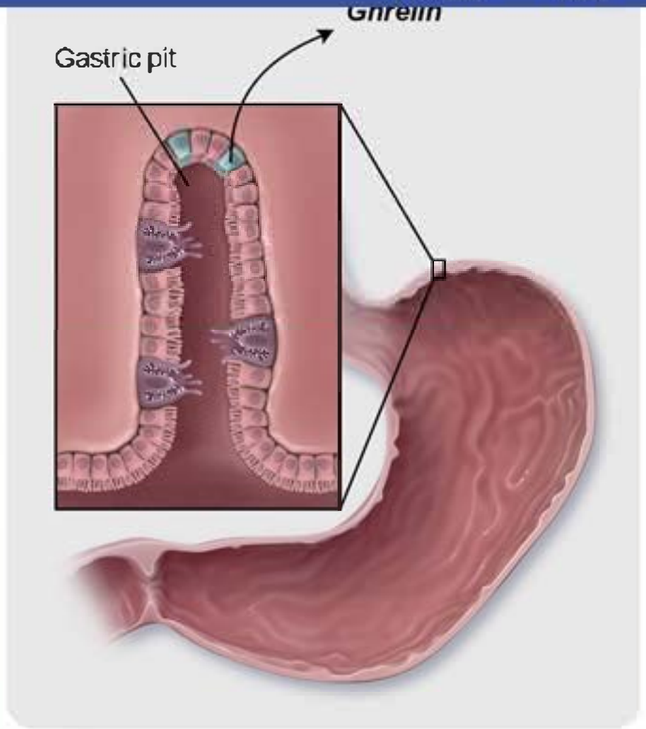

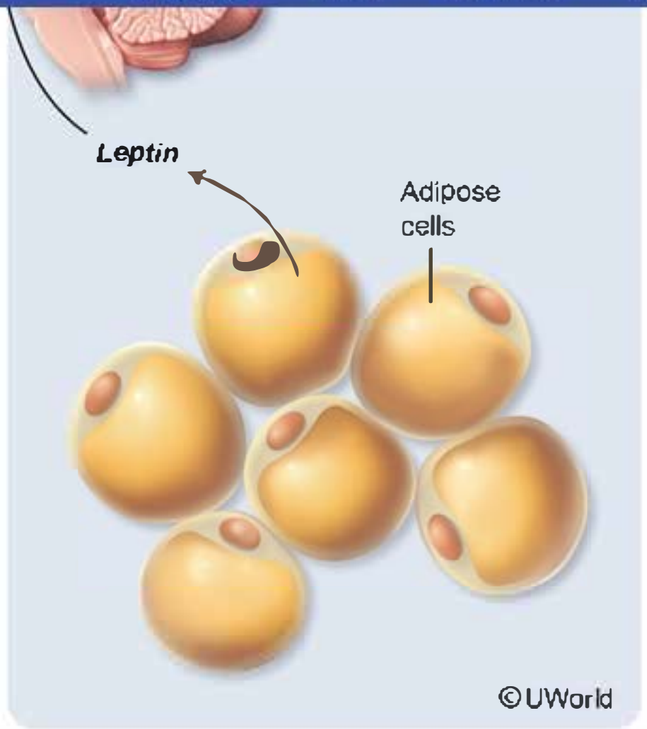

Energy homeostasis and body fat content are regulated by a complex network of hormones. Prominent hormones involved in weight regulation include:

- **Ghrelin:** Produced primarily in the stomach in response to fasting, ghrelin stimulates appetite and promotes weight gain.
- **Leptin:** Produced primarily by fat cells in response to short-term food intake and long-term adequacy of fat stores, leptin acts on the hypothalamus to decrease appetite (obesity blunts this action). During fasting states, leptin levels fall.
- **Insulin:** Produced by pancreatic beta cells in response to high blood glucose levels, insulin acts on the CNS to decrease appetite, in addition to its effects on glucose metabolism. Levels are higher and effects are blunted in obesity (insulin resistance); weight loss is associated with greater insulin sensitivity and lower insulin levels.

Caloric restriction and falling fat stores, as in these study subjects, lead to **increased ghrelin** levels along with **decreased insulin and leptin**

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Caloric restriction and falling fat stores, as in these study subjects, lead to **increased ghrelin** levels along with **decreased insulin and leptin** levels. This causes an increase in appetite and, typically, regain of weight. The effect can last up to a year or more and accounts for much of the difficulty patients have in maintaining short-term weight loss.

(Choice B) Certain bariatric procedures that alter stomach capacity (eg, sleeve gastrectomy) can induce weight loss with decreased ghrelin production (may reduce weight loss-associated appetite stimulation). However, dietary modification and exercise alone would lead to increased ghrelin secretion.

(Choice C) Overeating and weight gain suppress ghrelin secretion and increase secretion of leptin and insulin.

(Choice D) HIV-associated lipodystrophy is an alteration in fat distribution, most often seen in patients receiving highly active antiretroviral therapy. Numerous metabolic abnormalities have been seen in this disorder, including increased insulin levels, increased ghrelin, and decreased leptin secretion.

(Choice E) Fasting states that stimulate ghrelin and suppress insulin secretion generally lead to lower, not higher, leptin levels.

Educational objective:
Ghrelin stimulates appetite and promotes weight gain. Leptin and insulin act in the CNS to decrease appetite. Caloric restriction leads to increased ghrelin levels along with decreased insulin and leptin levels, causing an increase in appetite that can make it difficult to maintain weight loss.

A 34-year-old man comes to the office for a follow-up visit. The patient has had type 1 diabetes since age 12 and is diligent in taking insulin to achieve good glycemic control. Over the past few months, he has had more frequent episodes of hypoglycemia despite no changes in his treatment, diet, or physical activity, but the episodes have been associated with less severe hypoglycemic symptoms compared to prior episodes. Physical examination is unremarkable. Laboratory results show normal basic metabolic panel and serum TSH level. Hemoglobin A1c is 7.0%. Which of the following factors is primarily responsible for this patient's increased frequency of hypoglycemia?

A. Decreased epinephrine release

B. Decreased glucagon release

C. Decreased growth hormone release

D. Downregulation of insulin receptors

E. Upregulation of beta-adrenergic receptors

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A. Decreased epinephrine release (9%)

✓ B. Decreased glucagon release (38%)

C. Decreased growth hormone release (12%)

D. Downregulation of insulin receptors (19%)

E. Upregulation of beta-adrenergic receptors (20%)

Omitted
Correct answer
B

38%
Answered correctly

02 secs
Time Spent

05/26/2020
Last Updated

Explanation

Physiologic defense against hypoglycemia

↓ Insulin → ↓ Peripheral glucose utilization

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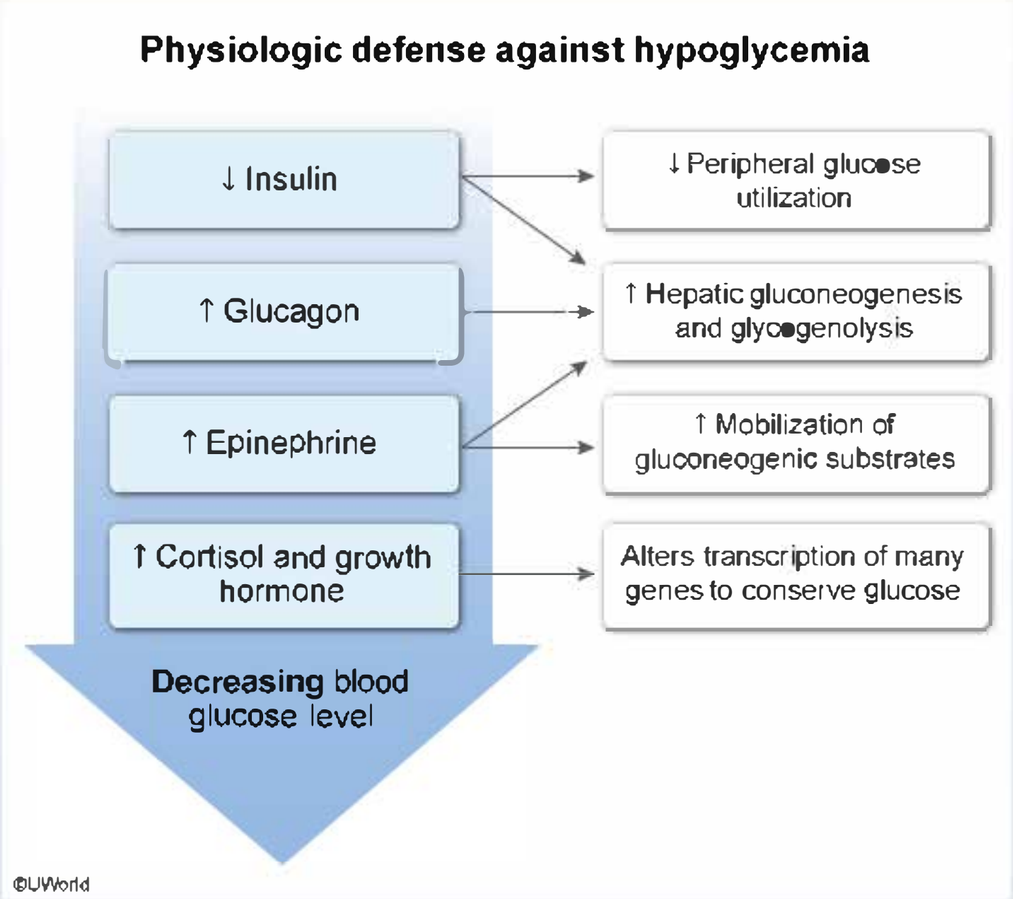

As blood glucose levels fall through the physiologic range, insulin secretion by pancreatic beta cells decreases, leading to reduced peripheral uptake and utilization of glucose. At the same time, alpha cells increase secretion of **glucagon**, which is the **primary counterregulatory hormone** to insulin and acts on the liver to rapidly increase glycogenolysis and gluconeogenesis and decrease glycolysis.

Patients with **type 1 diabetes mellitus** are at increased **risk of hypoglycemia** because **exogenous insulin** is not subject to the same regulation as endogenous insulin and will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes (ie, >5 years) frequently also have **alpha cell failure** with **decreased glucagon secretion** and therefore have an even greater risk of rapid

As blood glucose levels fall through the physiologic range, insulin secretion by pancreatic beta cells decreases, leading to reduced peripheral uptake and utilization of glucose. At the same time, alpha cells increase secretion of **glucagon**, which is the **primary counterregulatory hormone** to insulin and acts on the liver to rapidly increase glycogenolysis and gluconeogenesis and decrease glycolysis.

Patients with **type 1 diabetes mellitus** are at increased **risk of hypoglycemia** because **exogenous insulin** is not subject to the same regulation as endogenous insulin and will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes (ie, >5 years) frequently also have **alpha cell failure** with **decreased glucagon secretion** and therefore have an even greater risk of rapid hypoglycemia. Patients with pancreatogenic diabetes (eg, secondary to chronic pancreatitis) also typically have inadequate alpha cell reserve and can experience frequent hypoglycemia.

(Choice A) Progressive hypoglycemia prompts a catecholamine (eg, epinephrine) surge, which increases hepatic glucose production and triggers many of the characteristic hypoglycemic symptoms (eg, arousal, tremor). Patients with long-standing diabetes often have a blunted autonomic response to hypoglycemia, with **reduced hypoglycemic awareness**, but catecholamines are less important than glucagon in raising blood glucose levels.

(Choice C) Prolonged hypoglycemia can stimulate secretion of cortisol and growth hormone, which increase glucose levels. These hormones typically act over longer timescales (eg, days/weeks) and are less important than glucagon in preventing acute hypoglycemia.

(Choice D) Chronic exposure to high circulating insulin levels leads to downregulation of insulin receptors and reduced insulin sensitivity. This effect promotes hyperglycemia, not hypoglycemia.

(Choice E) Repeated hypoglycemia causes downregulation of beta-adrenergic receptors, which contributes to reduced hypoglycemic awareness. Depending on the systems involved, upregulation of beta-adrenergic receptors would generally reduce hypoglycemia and increase awareness.

Educational objective:
Patients with type 1 diabetes mellitus are at increased risk of hypoglycemia because exogenous insulin will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes may also have decreased glucagon secretion and therefore have an even greater risk of rapid hypoglycemia.

References

(ie, >5 years) frequently also have **alpha cell failure** with **decreased glucagon secretion** and therefore have an even greater risk of rapid hypoglycemia. Patients with pancreatogenic diabetes (eg, secondary to chronic pancreatitis) also typically have inadequate alpha cell reserve and can experience frequent hypoglycemia.

(Choice A) Progressive hypoglycemia prompts a catecholamine (eg, epinephrine) surge, which increases hepatic glucose production and triggers many of the characteristic hypoglycemic symptoms (eg, arousal, tremor). Patients with long-standing diabetes often have a blunted autonomic response to hypoglycemia, with **reduced hypoglycemic awareness**, but catecholamines are less important than glucagon in raising blood glucose levels.

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Educational objective:
Patients with type 1 diabetes mellitus are at increased risk of hypoglycemia because exogenous insulin will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes may also have decreased glucagon secretion and therefore have an even greater risk of rapid hypoglycemia.

References

- Mechanisms of hypoglycemia-associated autonomic failure in diabetes.

Physiology	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

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A 22-year-old primigravida who recently emigrated from the Dominican Republic has a normal vaginal delivery. The infant is phenotypically male but has hypospadias and a small phallus. The testes are well developed but reside in the inguinal area. His physical examination, including blood pressure, is otherwise normal. Serum testosterone level is within normal limits. A karyotype is performed and shows 46,XY. Which of the following enzymes is most likely deficient in this patient?

A. 5α-reductase

B. 17-hydroxylase

C. 21-hydroxylase

D. Aromatase

E. DHEA sulfatase

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- ✓ A. 5α-reductase (71%)
- B. 17-hydroxylase (8%)
- C. 21-hydroxylase (6%)
- D. Aromatase (6%)
- E. DHEA sulfatase (6%)

Omitted
Correct answer
A

71%
Answered correctly

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01/27/2020
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Explanation

5α-reductase deficiency

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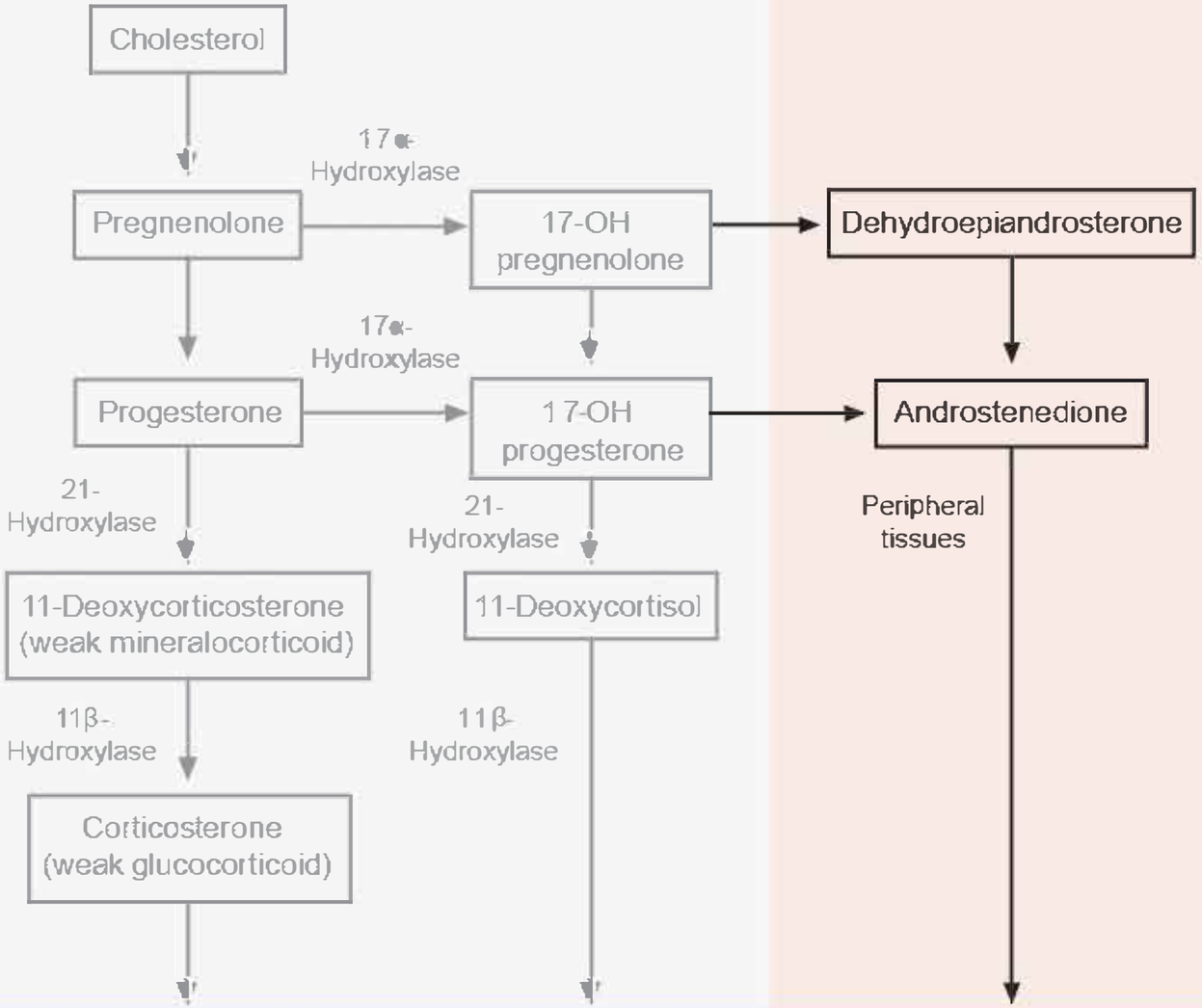
5α-reductase deficiency



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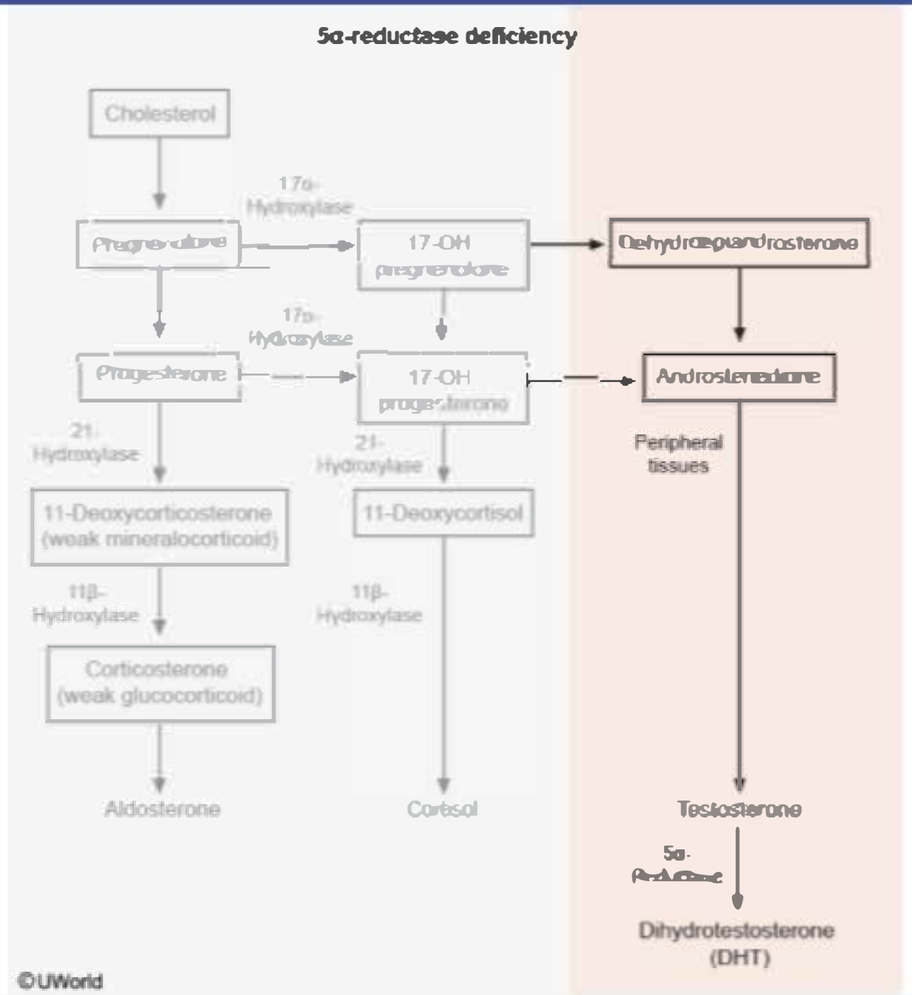

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Sexual development is influenced predominantly by 3 hormones:

- **Testosterone**: Development of internal male genitalia, spermatogenesis, male sexual differentiation at puberty (muscle mass, libido)
- **Dihydrotestosterone** (DHT): Development of external male genitalia, growth of prostate, male-pattern hair growth; also amplifies effects of testosterone due to high affinity for testosterone receptor.
- **Estrogen**: Endometrial proliferation, development of ovarian granulosa cells, breast development

5α-reductase converts testosterone to DHT. There are 2 types of 5α-reductase; type 1 is present in postpubescent skin, whereas type 2 is found predominantly in the genitals. Deficiency of **5α-reductase type 2** results in diminished conversion of testosterone to DHT in the male urogenital tract. In the male fetus with this genetic defect, the internal genitalia develop normally under the influence of testosterone, but the external genitalia do not develop properly due to the lack of DHT, resulting in **male pseudohermaphroditism**. The genitalia at birth can range from a small phallus with hypospadias to ambiguous or female-type genitalia. Such children are often raised as females until they reach puberty, when high levels of testosterone and the action of 5α-reductase type 1 result in masculinization with male-pattern muscle mass, voice deepening, penile and scrotal growth, and testicular descent.

(Choice B) Deficiency of 17-hydroxylase results in decreased secretion of cortisol and sex steroids and an increased level of mineralocorticoids. This deficiency manifests clinically with sodium retention, leading to hypertension and undervirilization of male infants (female-type genitalia).

(Choice C) 21-hydroxylase converts 17-hydroxyprogesterone to 11-deoxycortisol, and progesterone to 11-deoxycorticosterone. Deficiency of 21-hydroxylase causes corticosteroid precursors to be shunted toward androgen production, resulting in virilization of the female fetus and salt wasting. Male children have salt wasting and normal genitalia.

(Choice D) Aromatase catalyzes the conversion of androgens to estrogens in the gonads and peripheral tissues. Aromatase deficiency presents with virilization of female infants; male patients are not affected phenotypically.

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

Educational objective:
5α-reductase converts testosterone to dihydrotestosterone, which mediates development of the external genitalia in the male fetus. Male neonates with 5α-reductase deficiency are born with feminized external genitalia that typically masculinize at puberty. A small phallus and hypospadias are common.

tract. In the male fetus with this genetic defect, the internal genitalia develop normally under the influence of testosterone, but the external genitalia do not develop properly due to the lack of DHT, resulting in **male pseudohermaphroditism**. The genitalia at birth can range from a small phallus with hypospadias to ambiguous or female-type genitalia. Such children are often raised as females until they reach puberty, when high levels of testosterone and the action of 5α-reductase type 1 result in masculinization with male-pattern muscle mass, voice deepening, penile and scrotal growth, and testicular descent.

(Choice B) Deficiency of 17-hydroxylase results in decreased secretion of cortisol and sex steroids and an increased level of mineralocorticoids. This deficiency manifests clinically with sodium retention, leading to hypertension and undervirilization of male infants (female-type genitalia).

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Educational objective:

5α-reductase converts testosterone to dihydrotestosterone, which mediates development of the external genitalia in the male fetus. Male neonates with 5α-reductase deficiency are born with feminized external genitalia that typically masculinize at puberty. A small phallus and hypospadias are common.

References

- 5-Alpha reductase deficiency: a 40-year retrospective review.

Physiology	Endocrine, Diabetes & Metabolism	Sexual differentiation
Subject	System	Topic

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A 21-yearold man undergoes a routine pre-employment physical examination. During testicular examination, he is found to have only 1 testis in his scrotum. Further evaluation reveals an elevated serum FSH level and a normal serum LH level. Production of which of the following substances is likely to be impaired in this patient?

A. Testosterone

B. Dihydrotestosterone

C. DHEA

D. Inhibin B

E. Cortisol

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A 21-yearold man undergoes a routine preemployment physical examination. During testicular examination, he is found to have only 1 testis in his scrotum. Further evaluation reveals an elevated serum FSH level and a normal serum LH level. Production of which of the following substances is likely to be impaired in this patient?

A. Testosterone (10%)
B. Dihydrotestosterone (6%)
C. DHEA (3%)
✓ D. Inhibin B (78%)
E. Cortisol (0%)

Omitted
Correct answer
D

78%
Answered correctly

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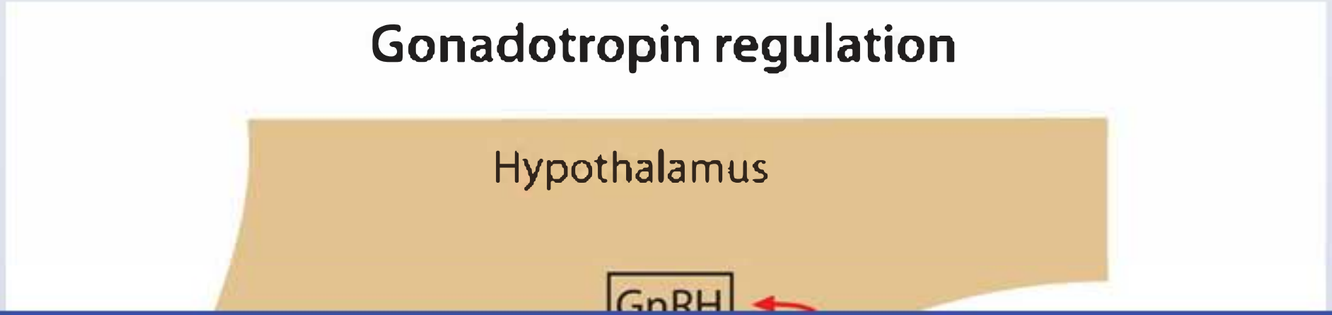
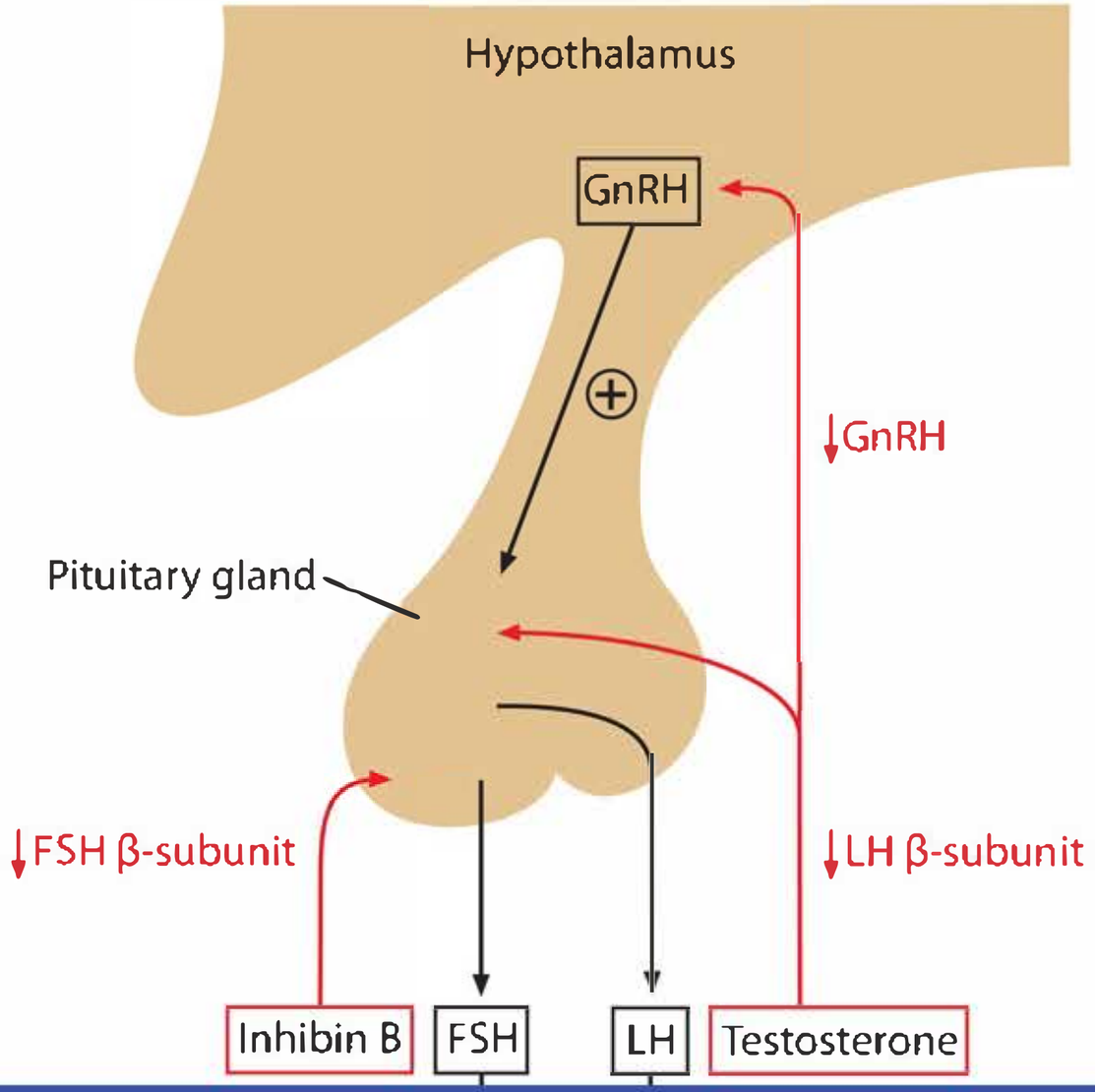
Time Spent

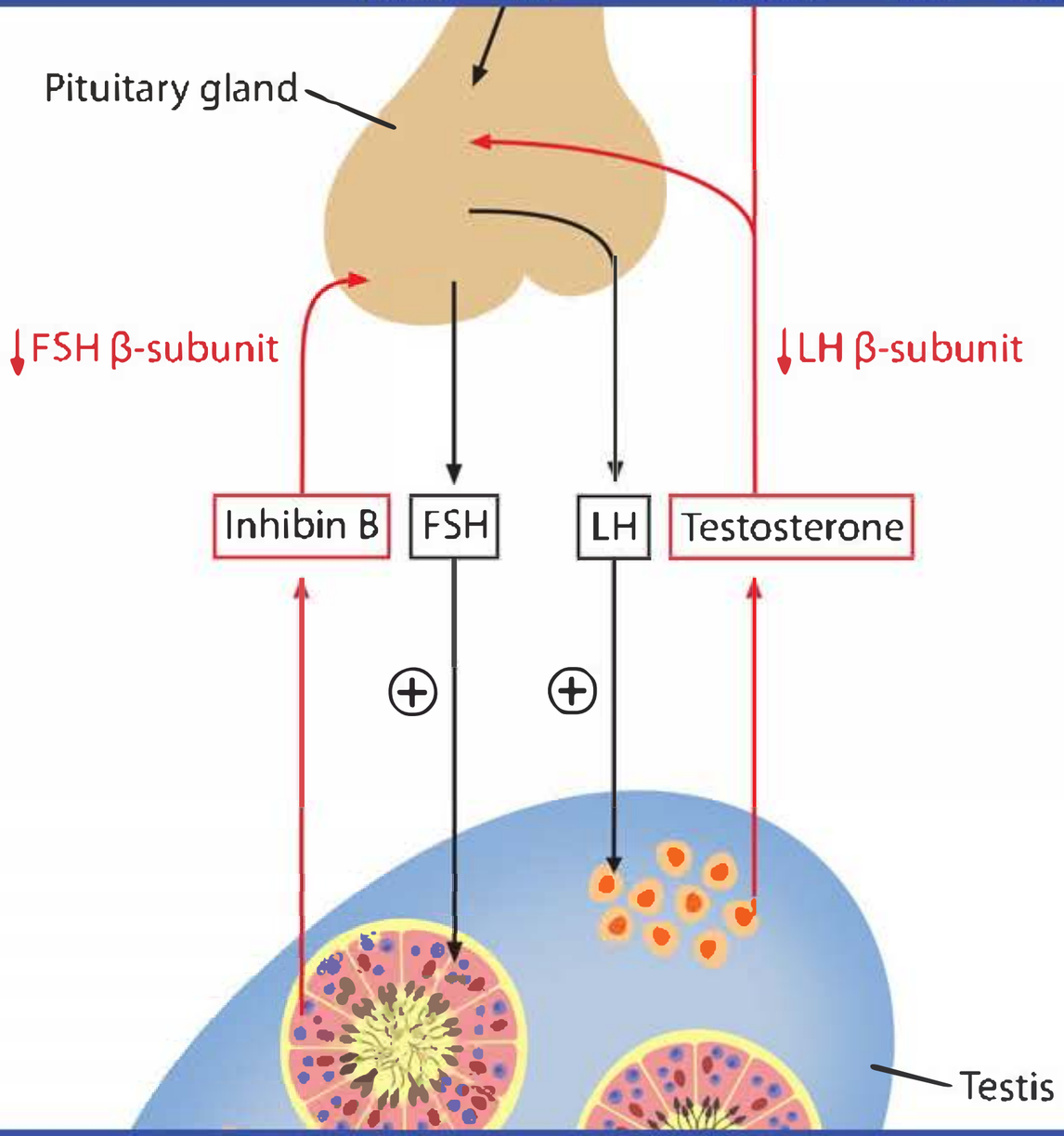
05/26/2020
Last Updated

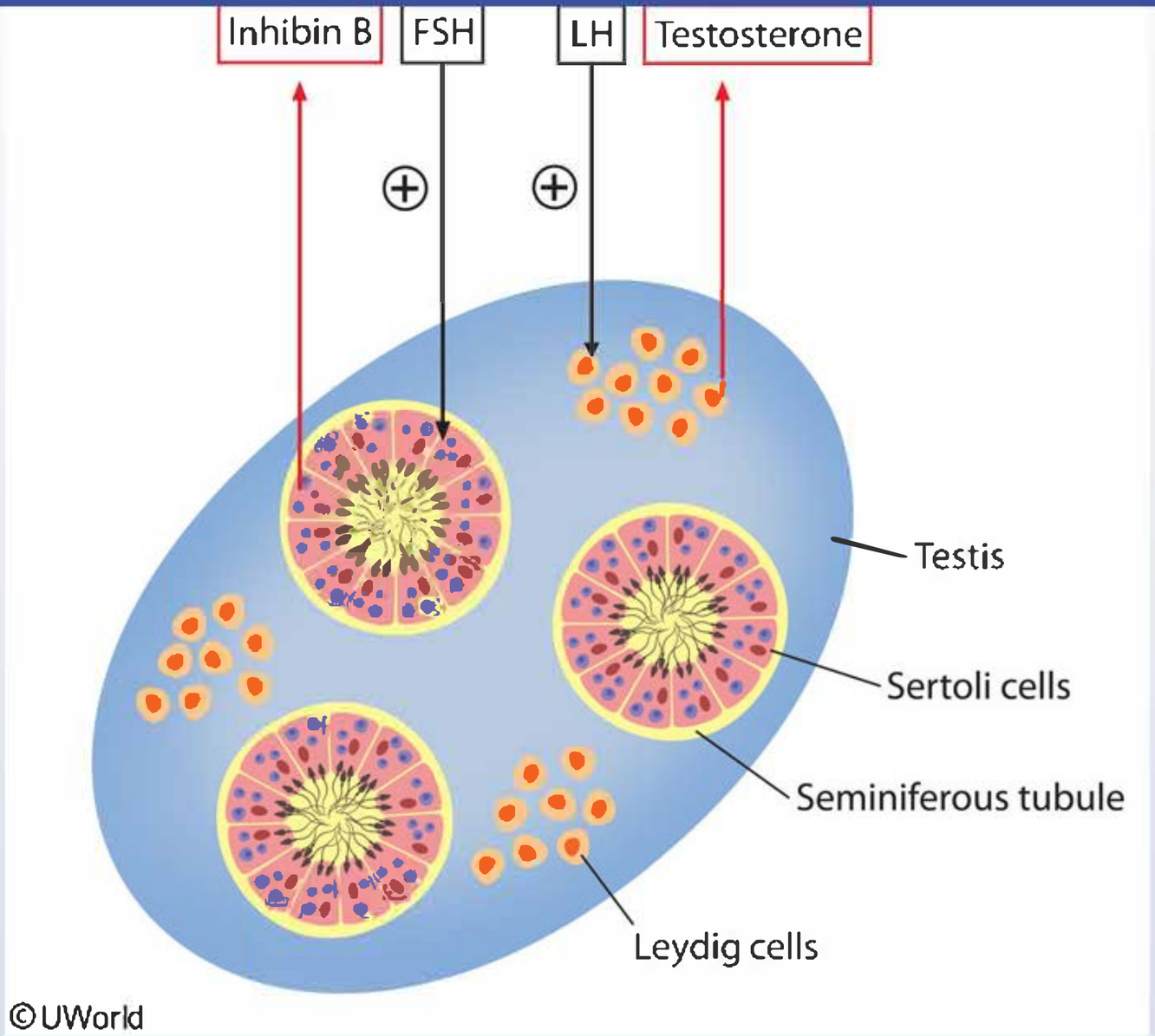
Explanation



Gonadotropin regulation




Pituitary gland
FSH β-subunit
LH β-subunit
Inhibin B
FSH
LH
Testosterone
Testis


Inhibin B
FSH
LH
Testosterone
Testis
Sertoli cells
Seminiferous tubule
Leydig cells
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Pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both FSH and LH are produced by the gonadotroph cells of the anterior pituitary. LH stimulates the release of testosterone from the Leydig cells of the testes; FSH stimulates the release of inhibin B from the Sertoli cells of the testes. Testosterone has a negative feedback effect on LH and GnRH secretion, and inhibin B suppresses FSH secretion.

Sertoli cells are present within the seminiferous tubules of the testes. In patients with 1 testicle, the mass of Sertoli cells is significantly reduced. Therefore, the circulating levels of inhibin B are likely to be low in these patients. Low inhibin B levels will not provide adequate negative feedback on FSH secretion, thus FSH levels will tend to be elevated in males who only have 1 testicle.

A male patient of any age who has only 1 testicle requires further evaluation. Since there is an increased cancer risk in men with an undescended testicle, most of these "abdominal testicles" are either removed (orchiectomy) or receive surgery that allows descent into the scrotum (orchiopexy).

(Choices A, B, and C) Although the number of Leydig cells is reduced when only 1 testicle is present, androgen levels are not affected due to compensation by the remaining Leydig cell mass. Additionally, this patient has a normal LH level, indicating that there is adequate androgenic feedback to the hypothalamus and pituitary. Testosterone, dihydrotestosterone, and DHEA cause LH feedback inhibition, but they are not part of the FSH feedback loop.

(Choice E) Cortisol has no direct relationship with LH and FSH secretion. High circulatory levels of cortisol, however, do produce hypogonadotropic hypogonadism by suppressing the release of gonadotrophinreleasing hormone.

Educational objective:
Inhibin B is produced by the Sertoli cells and is the physiological inhibitor of FSH secretion. LH concentration is controlled primarily by testosterone feedback.

Physiology	Endocrine, Diabetes & Metabolism	Cryptorchidism
Subject	System	Topic

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A 26-year-old man comes to the emergency department due to a 10-hour history of progressively worsening right-sided scrotal pain. Clinical and radiological evaluations confirm testicular torsion with significant ischemic damage and the patient undergoes unilateral orchiectomy. Three months later, he comes to the office for follow-up. The patient is otherwise healthy and takes no medications but is worried about the risk of sexual dysfunction and infertility. Further evaluation is most likely to show which of the following sets of findings in this patient?

	Erectile function	Sperm count
A.	Decreased	Decreased
B.	Normal	Decreased
C.	Normal	Normal
D.	Decreased	Normal

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	Erectile function	Sperm count
A. (1%)	Decreased	Decreased
✓ B. (59%)	Normal	Decreased
C. (38%)	Normal	Normal
D. (1%)	Decreased	Normal

Omitted
Correct answer
B

59%
Answered correctly

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Last Updated

Explanation

Gonadotropin regulation

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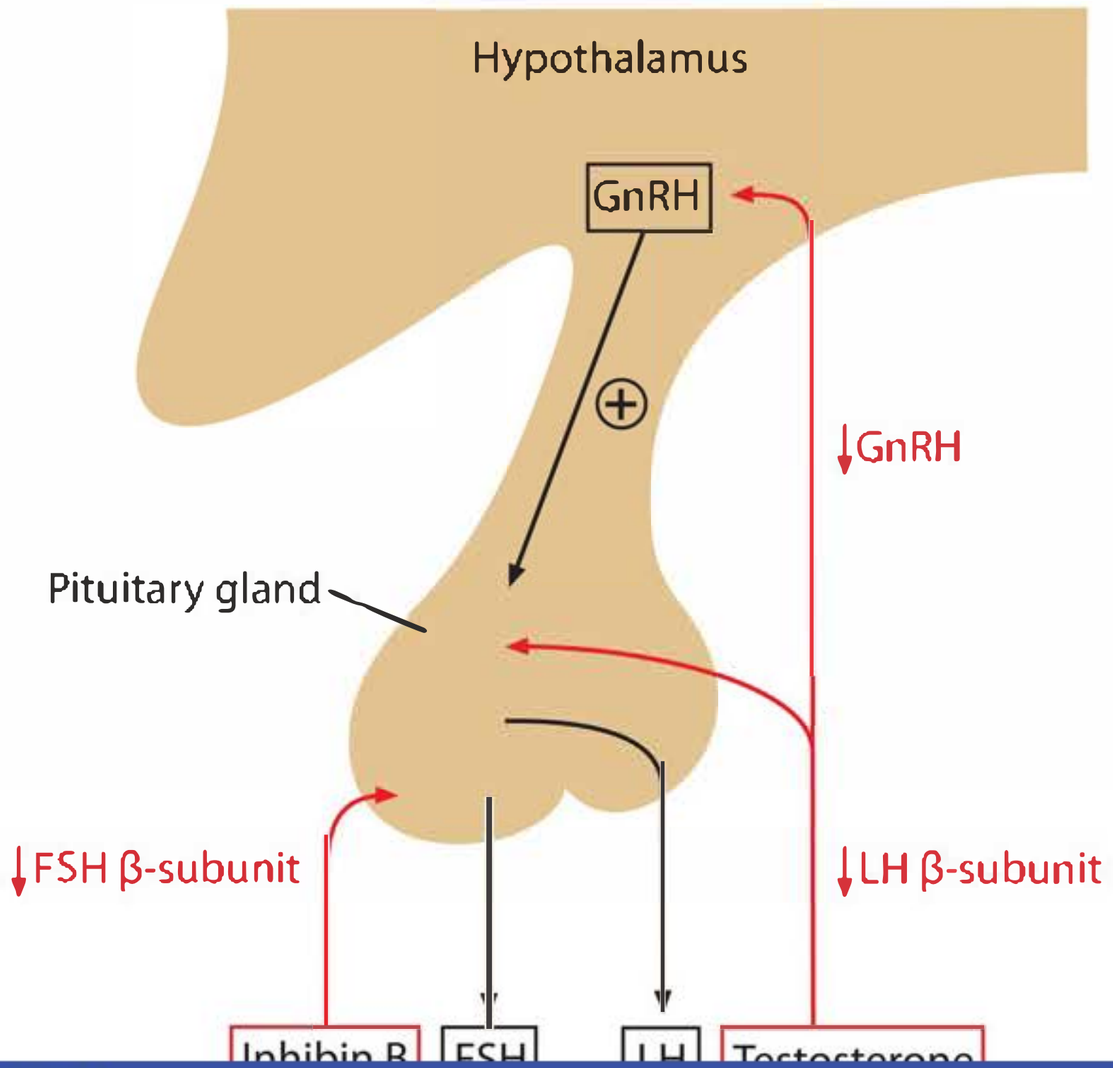
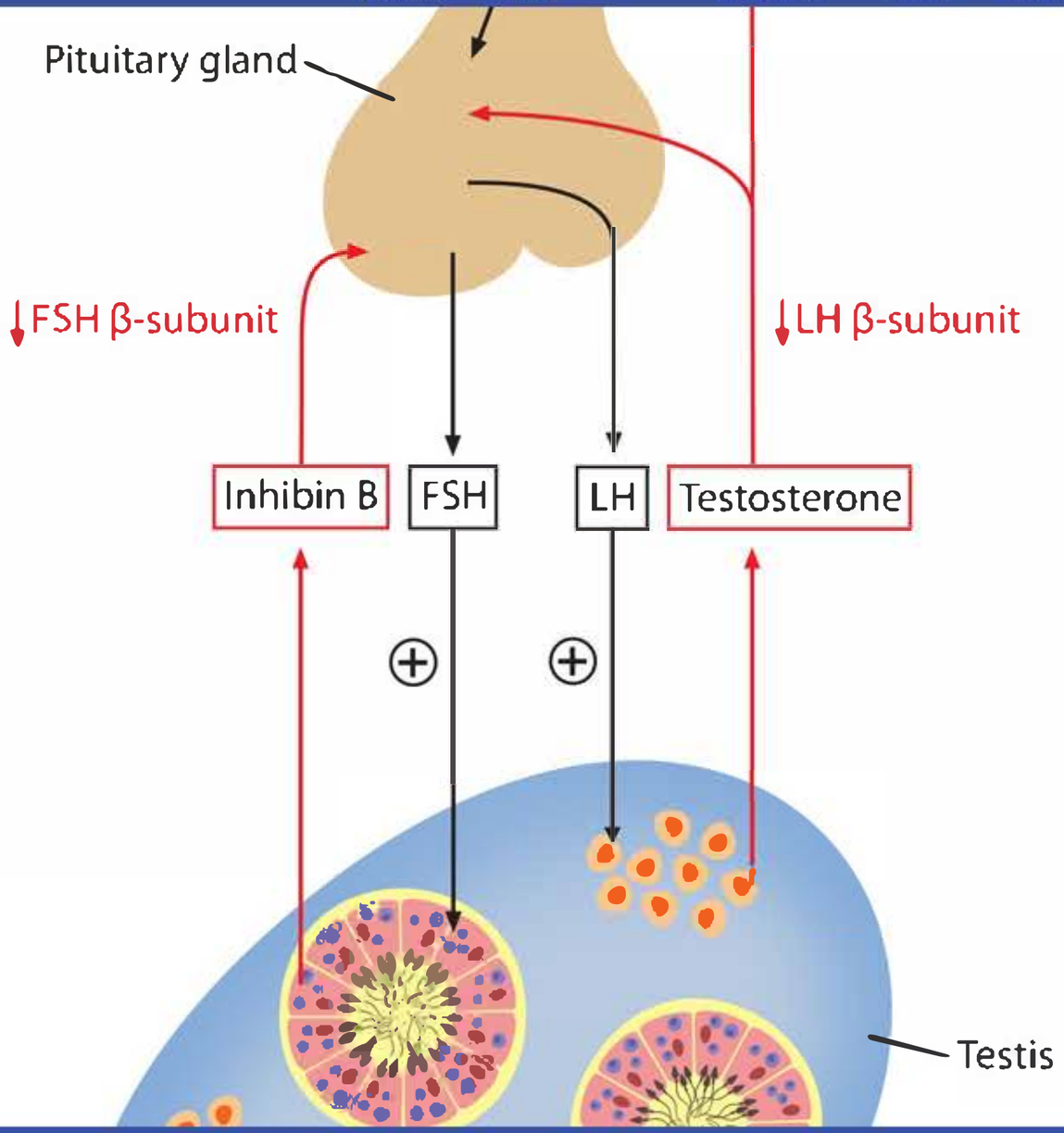
Gonadotropin regulation




Pituitary gland
FSH β-subunit
LH β-subunit
Inhibin B
FSH
LH
Testosterone
Testis

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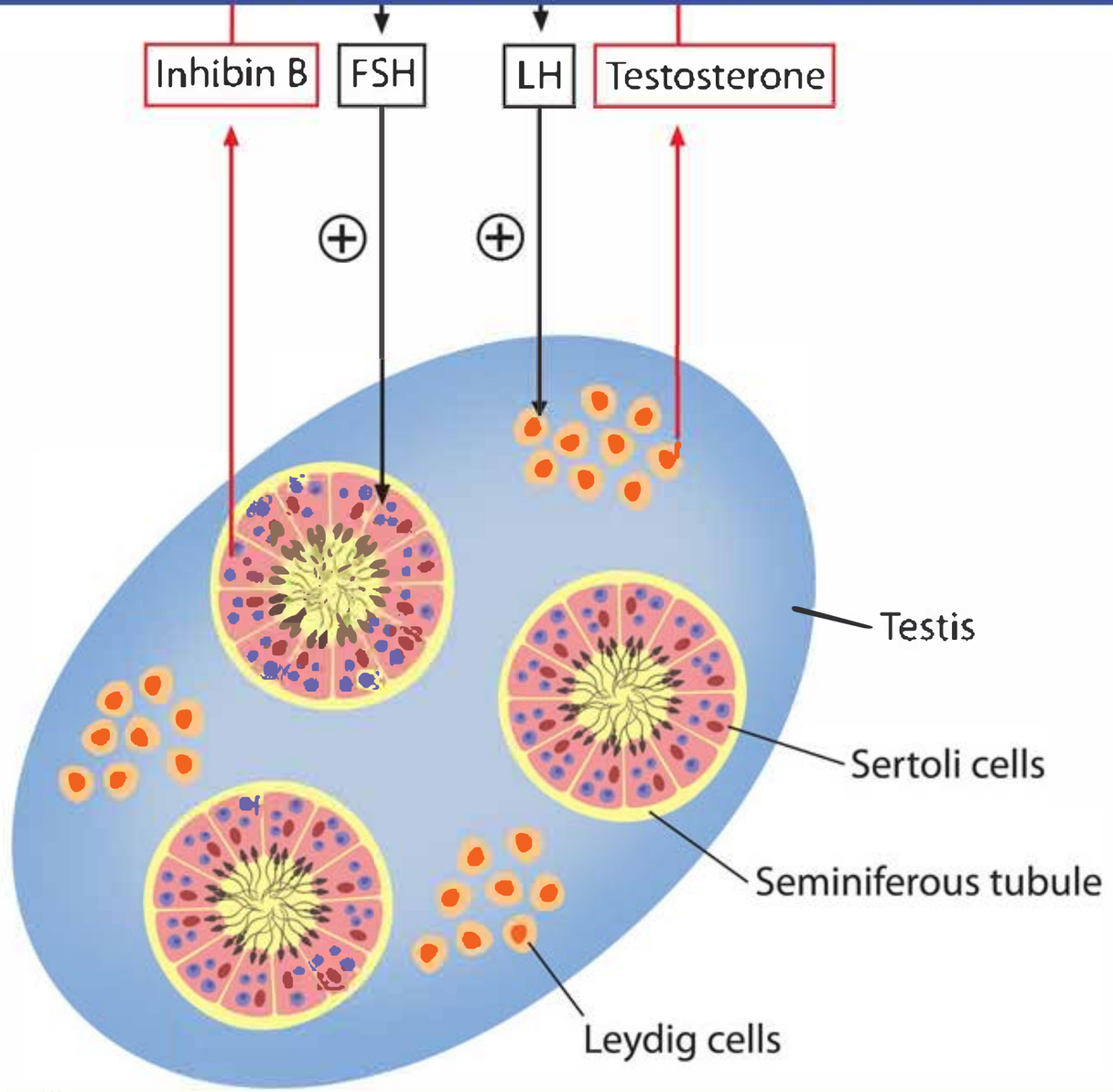

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Spermatogenesis in the testis is dependent on 2 primary hormone systems. Testicular Leydig cells produce **testosterone** in response to LH from the pituitary; in turn, LH is regulated by feedback inhibition from testosterone. At the same time, FSH from the pituitary induces the Sertoli cells to produce androgen binding protein (ABP), which concentrates testosterone in the seminiferous tubules and facilitates spermatogenesis. The Sertoli cells also produce inhibin, which provides feedback regulation of FSH.

Following **unilateral orchiectomy**, the initial drop in circulating testosterone stimulates pituitary LH secretion, leading to **compensatory testosterone production** and Leydig cell hyperplasia in the remaining testis. Testosterone levels are quickly restored, maintaining normal libido, erectile function, and secondary sex characteristics.

Concurrently, the loss of inhibin following unilateral orchiectomy leads to increased pituitary FSH release, stimulating ABP production and facilitating spermatogenesis in the remaining testis. However, due to the **loss of seminiferous tubules** in the orchiectomized testis, most patients experience **decreased net spermatogenesis**, often with reduced fertility **(Choice C)**.

(Choice A) Bilateral testicular damage (eg, orchitis, bilateral orchiectomy) leads to azoospermia. In addition, nontesticular sources of testosterone (eg, adrenals) are often inadequate to maintain normal libido and erectile function.

(Choice D) Erectile dysfunction (ED) with normal sperm counts can be caused by a variety of disorders (eg, neurologic or vascular disorders, psychogenic ED), but most patients who have loss of testosterone production severe enough to cause ED will also have impaired spermatogenesis.

Educational objective:
Following unilateral orchiectomy, the drop in testosterone stimulates pituitary LH secretion, which stimulates increased testosterone production in the remaining testis and maintains libido, erectile function, and secondary sex characteristics. However, the loss of sperm-producing tissue usually causes a drop in sperm counts.

Physiology	Endocrine, Diabetes & Metabolism	Male sexual dysfunction
Subject	System	Topic

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Physiology	Endocrine, Diabetes & Metabolism	Male sexual dysfunction
Subject	System	Topic

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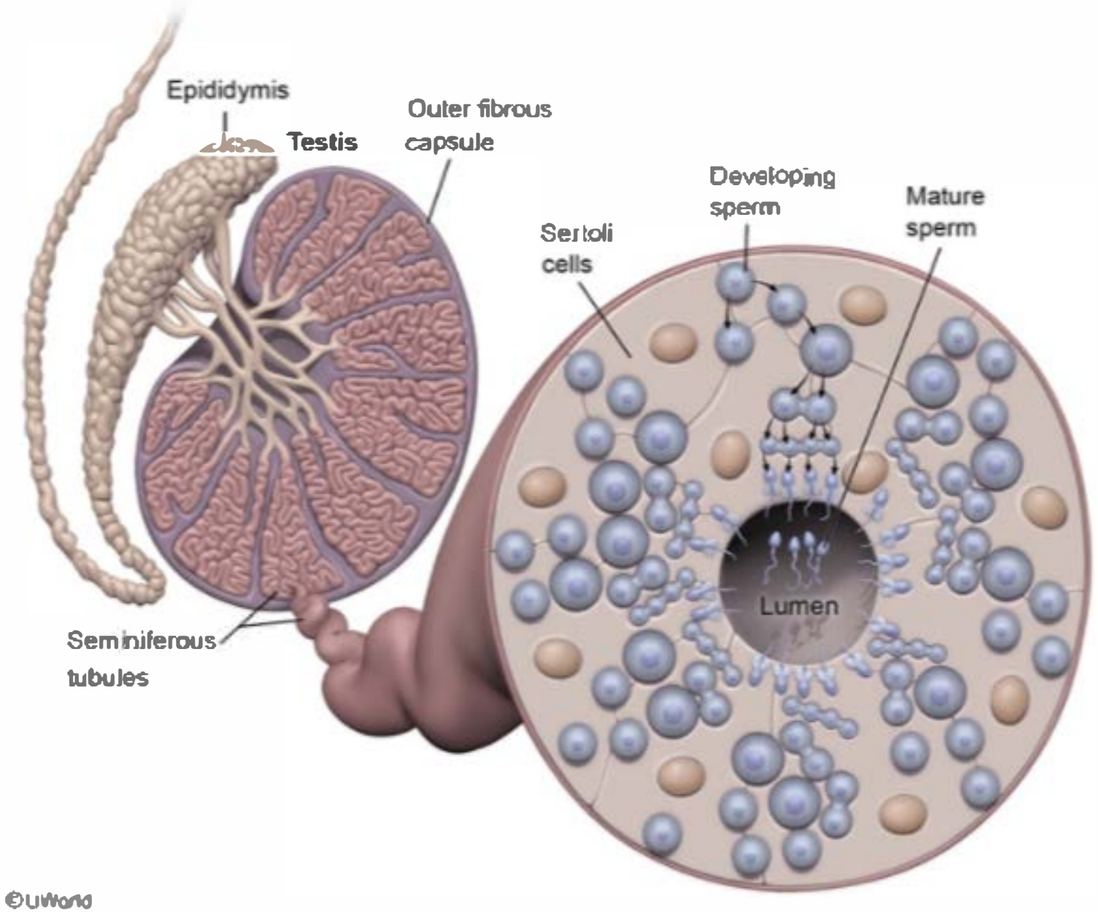
Spermatogenesis



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A 14-year-old boy is brought to the emergency department after accidental ingestion of a chicken bone that lodged in his esophagus. Upper endoscopy is performed and the bone is successfully removed. However, the patient is incidentally found to have mild hypercalcemia on laboratory testing. On follow-up with his primary care provider 2 weeks later, he has no symptoms and clinical examination is unremarkable. Further questioning reveals that several of his family members also have mild hypercalcemia. Subsequent laboratory studies show a borderline high parathyroid hormone concentration, very low urinary calcium level, and normal 25-hydroxyvitamin D level. A mutation in which of the following receptors is most likely responsible for this patient's laboratory abnormalities?

A. Intracellular receptor with a DNA-binding domain

B. Membrane-bound receptor coupled with a G protein

C. Transmembrane ligand-gated ion channel

D. Transmembrane receptor associated with intrinsic tyrosine kinase activity

E. Transmembrane receptor causing activation of Janus kinase/STAT pathway

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- A. Intracellular receptor with a DNA-binding domain (7%)
- ✓ B. Membrane-bound receptor coupled with a G protein (55%)
- C. Transmembrane ligand-gated ion channel (20%)
- D. Transmembrane receptor associated with intrinsic tyrosine kinase activity (9%)
- E. Transmembrane receptor causing activation of Janus kinase/STAT pathway (7%)

Omitted
Correct answer
B

55%
Answered correctly

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03/31/2020
Last Updated

Explanation

Calcium homeostasis

Normal sensitivity to Ca^{2+}

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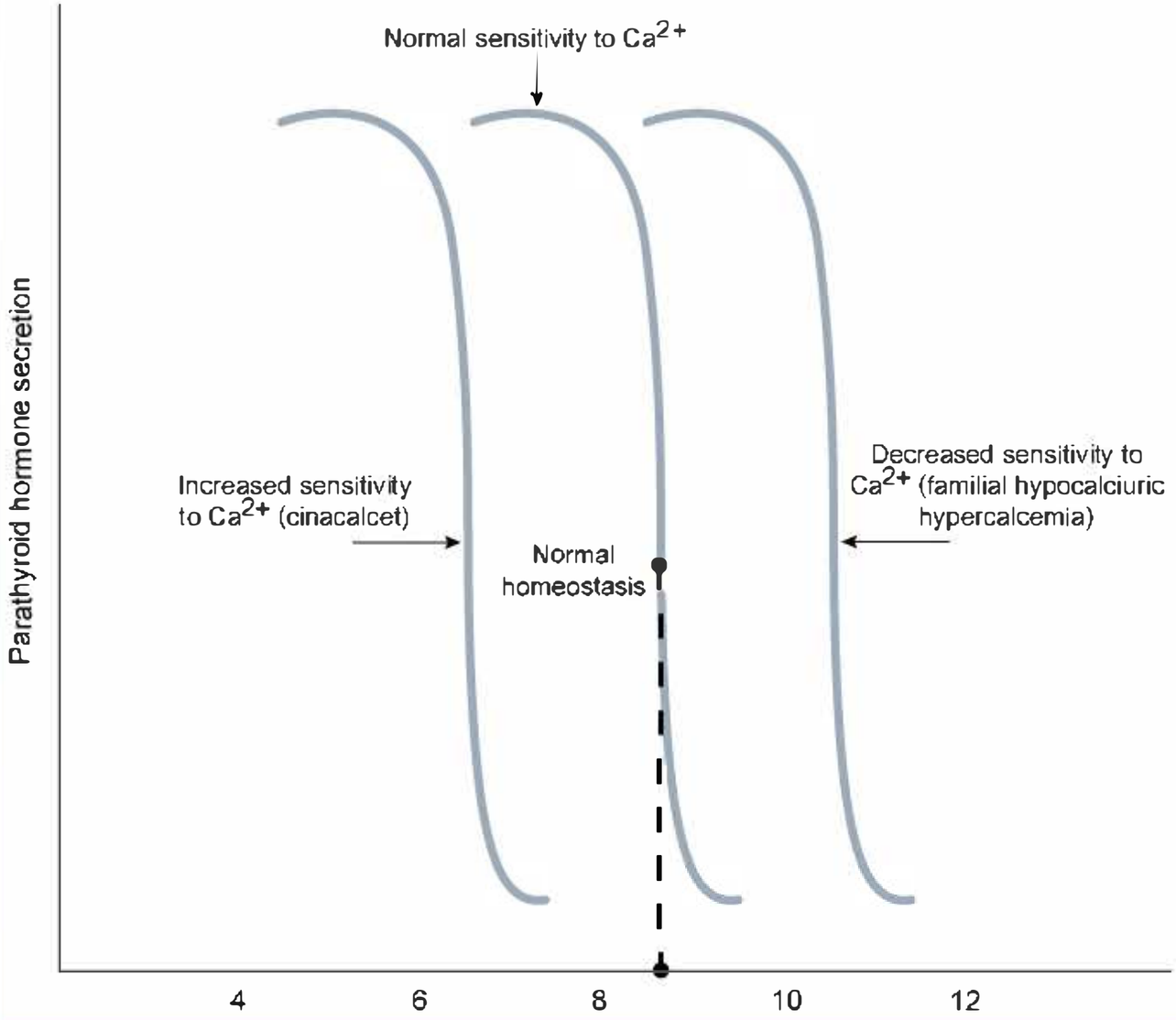
Calcium homeostasis



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Calcium-sensing receptors (CaSRs) are transmembrane **G_q protein–coupled** (metabotropic) receptors that regulate the secretion of parathyroid hormone (PTH) in response to changes in circulating calcium levels. Binding of calcium to CaSRs leads to the inhibition of PTH release, whereas low calcium levels allow increased PTH release.

Familial hypocalciuric hypercalcemia (FHH) is a benign autosomal dominant disorder caused by defective CaSRs in the parathyroid gland and kidneys. In FHH, higher serum calcium levels are required to suppress the secretion of PTH. This raises the set point of calcium-induced regulation of PTH secretion. Patients with FHH have mild asymptomatic hypercalcemia, reduced urinary excretion of calcium, and high normal or mildly elevated PTH.

(Choice A) Steroid hormones, thyroid hormone, and vitamin D act by binding to intracellular receptors with DNA-binding domains that interact with the regulatory DNA sequences of target genes.

(Choice C) Transmembrane ligand-gated ion channels (ionotropic receptors) allow a regulated flux of calcium, sodium, potassium, and chloride ions across the cell membrane. Neurotransmitters that work via ion channel–linked receptors include acetylcholine, serotonin, N-methyl-D-aspartate, and gamma-aminobutyric acid.

(Choice D) Insulin and insulin-like growth factor work by stimulating transmembrane receptors with intrinsic tyrosine kinase activity in the intracellular domain, initiating a downstream phosphorylation cascade.

(Choice E) Janus kinase (JAK) is a cytoplasmic protein activated by ligand binding to transmembrane receptors. JAKs activate cytoplasmic transcription factors called signal transducers and activators of transcription (STAT), which enter the nucleus to promote gene transcription. Examples of hormones using a JAK/STAT messenger system include erythropoietin, growth hormone, and prolactin.

Educational objective:
Calcium-sensing receptors are G protein–coupled receptors that regulate the secretion of parathyroid hormone in response to changes in circulating calcium levels. Familial hypocalciuric hypercalcemia is a benign autosomal dominant disorder caused by defective calcium-sensing receptors in the parathyroid gland and kidneys.

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Familial hypocalciuric hypercalcemia (FHH) is a benign autosomal dominant disorder caused by defective CaSRs in the parathyroid gland and kidneys. In FHH, higher serum calcium levels are required to suppress the secretion of PTH. This raises the set point of calcium-induced regulation of PTH secretion. Patients with FHH have mild asymptomatic hypercalcemia, reduced urinary excretion of calcium, and high normal or mildly elevated PTH.

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Educational objective:
Calcium-sensing receptors are G protein–coupled receptors that regulate the secretion of parathyroid hormone in response to changes in circulating calcium levels. Familial hypocalciuric hypercalcemia is a benign autosomal dominant disorder caused by defective calcium-sensing receptors in the parathyroid gland and kidneys.

References

- Familial hypocalciuric hypercalcaemia: a review.

Physiology	Endocrine, Diabetes & Metabolism	Hypercalcemia
Subject	System	Topic

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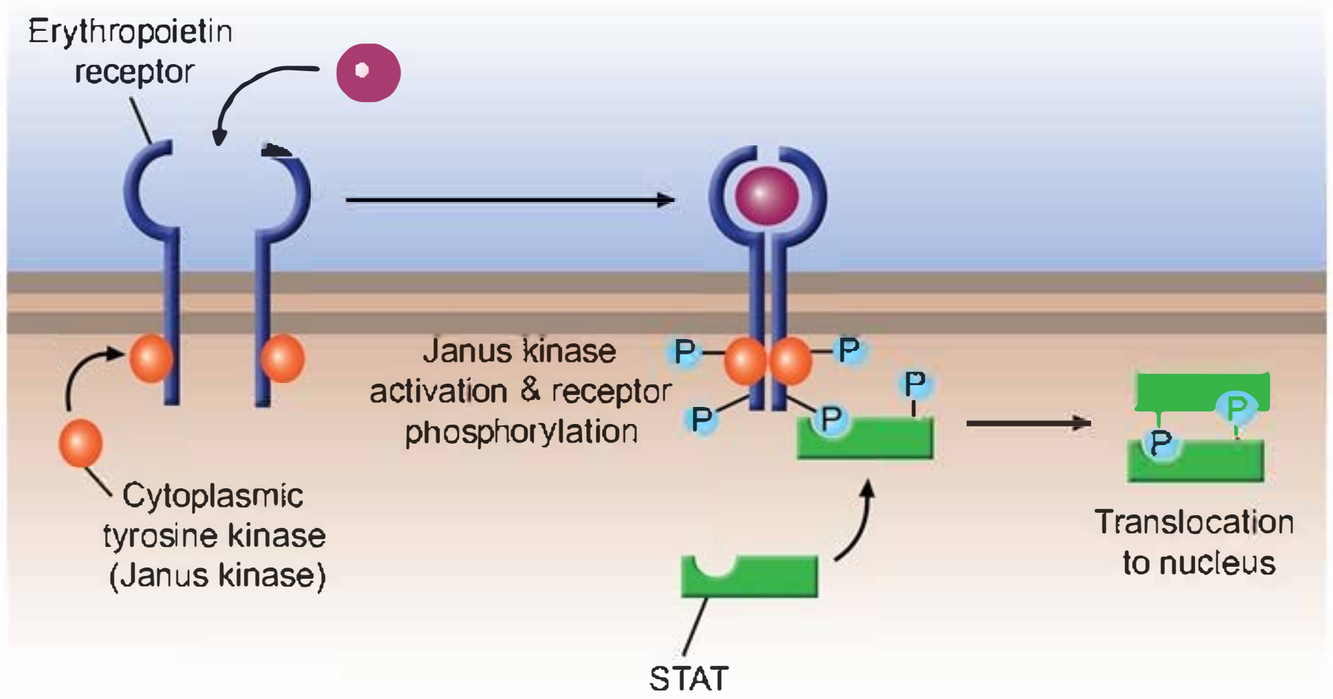
Familial hypocalciuric hypercalcemia (FHH) is a benign autosomal dominant disorder caused by defective CaSRs in the parathyroid gland and

Exhibit Display

Erythropoietin signal transduction



STAT = signal transducers and activators of transcription.

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An individual with a point mutation affecting the gene responsible for neurophysin synthesis is most likely to suffer from:

A. Short stature

B. Hyperpigmentation

C. Diabetes insipidus

D. Hypothyroidism

E. Infertility

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An individual with a point mutation affecting the gene responsible for neurophysin synthesis is most likely to suffer from:

A. Short stature (8%)

B. Hyperpigmentation (11%)

✓ C. Diabetes insipidus (69%)

D. Hypothyroidism (4%)

E. Infertility (5%)

Omitted
Correct answer
C

69%
Answered correctly

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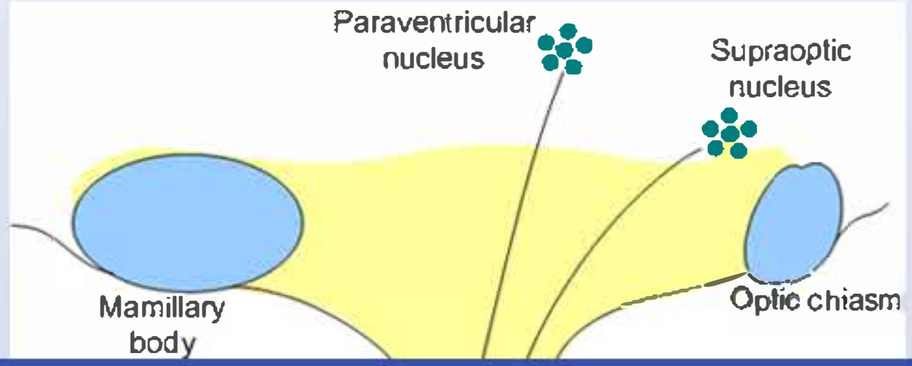
02/03/2020
Last Updated

Explanation



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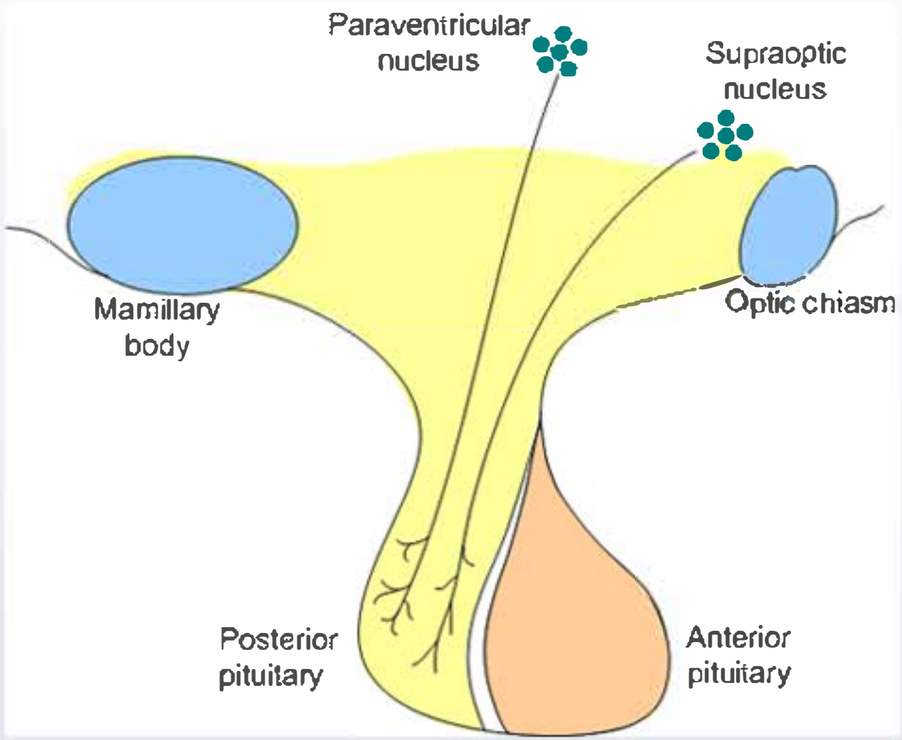

Neurophysins are carrier proteins for oxytocin and vasopressin (antidiuretic hormone, ADH), hormones produced within the paraventricular and supraoptic nuclei, respectively, and released from the posterior pituitary. Like the hormones they accompany, neurophysins are produced within the neuronal cell bodies of hypothalamic nuclei. Neurophysins bind oxytocin and vasopressin and act as chaperone molecules as they are shuttled toward the nerve terminals in the posterior pituitary.

Neurophysin II has a binding site specific for vasopressin and is thought to be involved in the transport and packaging of vasopressin through the endoplasmic reticulum (ER) and Golgi apparatus into neurosecretory granules. A point mutation in neurophysin II could result in abnormal protein folding and removal from the ER along with bound vasopressin, thereby decreasing availability of vasopressin for neurosecretory release. Such a mechanism may be responsible for some cases of autosomal dominant hereditary hypothalamic diabetes insipidus.

(Choice A) Short stature may result from a growth hormone deficiency. Neither hypothalamic GHRH release nor anterior pituitary growth

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(Choice A) Short stature may result from a growth hormone deficiency. Neither hypothalamic GHRH release nor anterior pituitary growth hormone secretion involves neurophysins.

(Choice B) Generalized hyperpigmentation is a manifestation of Addison's disease, where a primary defect in adrenal cortisol production reduces feedback inhibition of anterior pituitary pro-opiomelanocortin (POMC) synthesis. As a result, POMC cleavage products, including ACTH and melanocyte-stimulating hormone (MSH), are secreted in excess. High MSH levels cause increased melanin synthesis by melanocytes.

(Choice D) The synthesis and release of TRH and TSH do not involve neurophysins. TRH stimulates the release of both TSH and prolactin. Dopamine tonically inhibits prolactin release.

(Choice E) Infertility can result from inadequate hypothalamic release of GnRH or decreased anterior pituitary production of FSH or LH.

Educational Objective:
Neurophysins are carrier proteins for oxytocin and vasopressin (ADH). Oxytocin and vasopressin are carried by unique neurophysins from their site of production in the cell bodies of the paraventricular and supraoptic nuclei to their site of release in the axon terminals of the posterior pituitary. Point mutations in neurophysin II underlie most cases of hereditary hypothalamic diabetes insipidus, a disorder resulting from insufficient ADH release into the systemic circulation.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes insipidus
Subject	System	Topic

supraoptic nuclei, respectively, and released from the posterior pituitary. Like the hormones they accompany, neurophysins are produced within the neuronal cell bodies of hypothalamic nuclei. Neurophysins bind oxytocin and vasopressin and act as chaperone molecules as they are shuttled toward the nerve terminals in the posterior pituitary.

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Physiology	Endocrine, Diabetes & Metabolism	Diabetes insipidus
Subject	System	Topic

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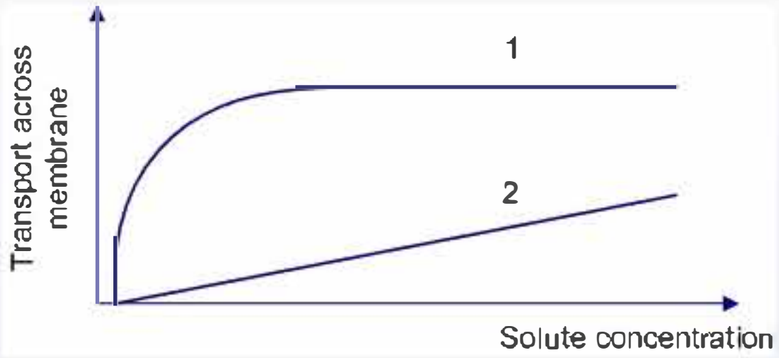
Two graphs illustrating the transport rate of solutes across the plasma membrane are shown on the slide below.



Which of the following best explains the difference in the shape of the curves?

A. Different amounts of membrane surface area for diffusion

B. Different degrees of membrane thickness

C. The 2 solutes have different molecular weights

D. The 2 solutes have different oil/water partition coefficients

E. The presence of a protein transporter

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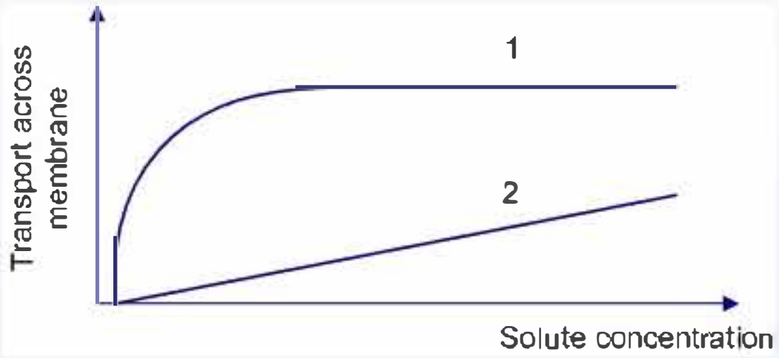

Which of the following best explains the difference in the shape of the curves?

A. Different amounts of membrane surface area for diffusion (3%)

B. Different degrees of membrane thickness (1%)

C. The 2 solutes have different molecular weights (3%)

D. The 2 solutes have different oil/water partition coefficients (10%)

✓ E. The presence of a protein transporter (80%)

Omitted
Correct answer
E

80%
Answered correctly

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Explanation

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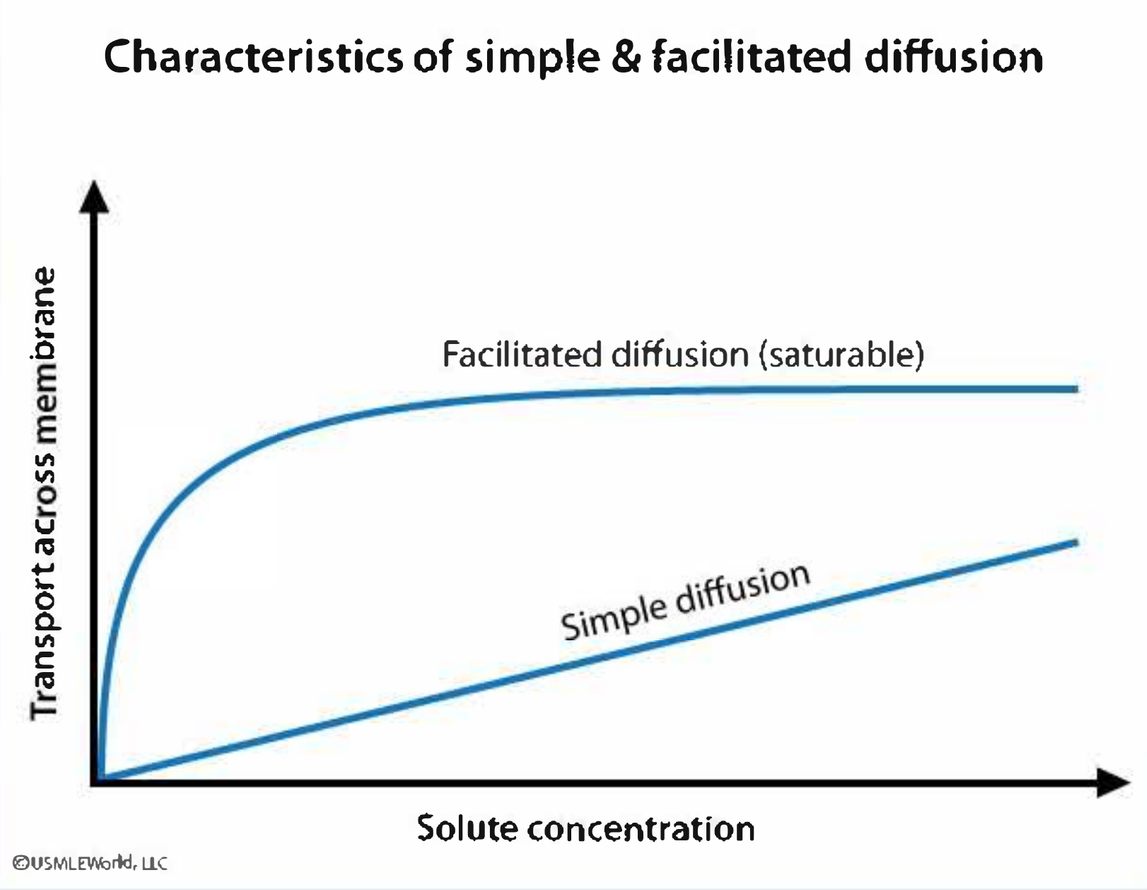

The image above illustrates the difference between the rate of transport of solute across the cell membrane in **simple diffusion** (line 2) and **carrier-mediated transport** (line 1).

There are two types of diffusion:

- Simple diffusion – molecules move through a membrane without the help of carrier proteins.
- Facilitated diffusion – requires carrier proteins.

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Solute concentration

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There are two types of diffusion:

- Simple diffusion – molecules move through a membrane without the help of carrier proteins.
- Facilitated diffusion – requires carrier proteins.

Carrier proteins are typically transmembrane proteins that possess binding sites for the substrate they transport. Binding is followed by movement of the substrate across the cell membrane to the intracellular space, where it is released into the cytoplasm. Because there is a finite number of carrier proteins in the cell membrane, **transporter saturation** occurs with facilitated diffusion, and can be seen as a **flattening of the curve** (maximum diffusion speed), even as solute concentration continues to increase. This maximum rate of transport is referred to as the transport maximum (T_m) and is similar in principle to the V_{max} in standard enzyme kinetics.

(Choices A, B, C, D) These other factors are important for determining the rate of diffusion (ie, slope of the line), but would not explain the flattening of the curve in line 1 (which is best accounted for by saturation of a protein carrier). In general, the rate of diffusion increases with:

- Higher concentration gradients across the membrane
- Lower molecular weight
- Larger diffusion surface area
- Thinner membrane thickness

For molecules that move through the membrane via simple diffusion, the degree of lipophilicity is also important; molecules with a high oil-water partition coefficient are more easily able to cross the membrane and will diffuse faster.

Educational objective:
Carrier-mediated transport includes facilitated diffusion and active transport. Movement of substrate across the cell membrane by these mechanisms depends on the presence of carrier proteins that can become saturated at high substrate concentrations.

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Physiology	General Principles	Cellular transports
Subject	System	Topic

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A 36-year-old man with type 1 diabetes mellitus comes to the office due to recurrent hypoglycemic episodes. He previously had difficulty controlling his high blood glucose levels, but over the past several weeks his blood glucose has intermittently dropped to <50 mg/dL with accompanying symptoms of tremulousness and headache. There have been no recent changes in his diet, activity level, insulin dosage, or other medical therapy. The patient's other medical conditions include chronic kidney disease from diabetic nephropathy. His estimated glomerular filtration rate has declined to 20 mL/min in recent months, and he is under consideration for initiation of hemodialysis. Physical examination findings are unchanged from the previous office visit 3 months ago. Which of the following is most likely contributing to this patient's current glycemic disturbances?

A. Decreased hepatic glucose production
B. Decreased renal insulin clearance
C. Increased pancreatic insulin secretion
D. Increased renal glucose excretion
E. Increased tissue insulin sensitivity

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A. Decreased hepatic glucose production (4%)
✓ B. Decreased renal insulin clearance (59%)
C. Increased pancreatic insulin secretion (1%)
D. Increased renal glucose excretion (32%)
E. Increased tissue insulin sensitivity (1%)

Omitted
Correct answer
B

59%
Answered correctly

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Last Updated

Explanation

Insulin is a peptide hormone that has both **renal and hepatic clearance**. Degradation of circulating insulin in the kidneys is dependent on an adequate glomerular filtration rate (GFR), which allows for delivery of insulin to the proximal tubule cells where it is broken down. **Chronic kidney disease** (CKD) causes **decreased GFR**, which impairs insulin clearance.

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Explanation

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In patients with normal pancreatic function, hypoglycemia is avoided because pancreatic insulin production decreases and circulating insulin levels rapidly return to baseline. However, patients taking **exogenous insulin** are at increased **risk of hypoglycemia** if there is no decrease in dosage to compensate for renal failure.

In light of this patient's worsening CKD, his symptomatic hypoglycemia is likely due to **reduced renal insulin clearance** and a prolonged insulin effect.

(Choice A) Advanced CKD leads to reduced gluconeogenesis in the kidney, not the liver. Hepatic gluconeogenesis is inhibited by inflammatory cytokine release (eg, sepsis), heavy alcohol use, and beta blockers.

(Choice C) Patients with type 1 diabetes typically have minimal to no secretory reserve and cannot increase insulin in response to physiologic stimuli.

(Choice D) Increased renal glucose excretion can cause glucosuria; however, this occurs in the setting of significant hyperglycemia (not hypoglycemia). In addition, this patient's low glomerular filtration rate would be expected to reduce renal glucose excretion.

(Choice E) Insulin sensitivity is decreased (not increased) in CKD due to the accumulation of urea and other metabolic toxins.

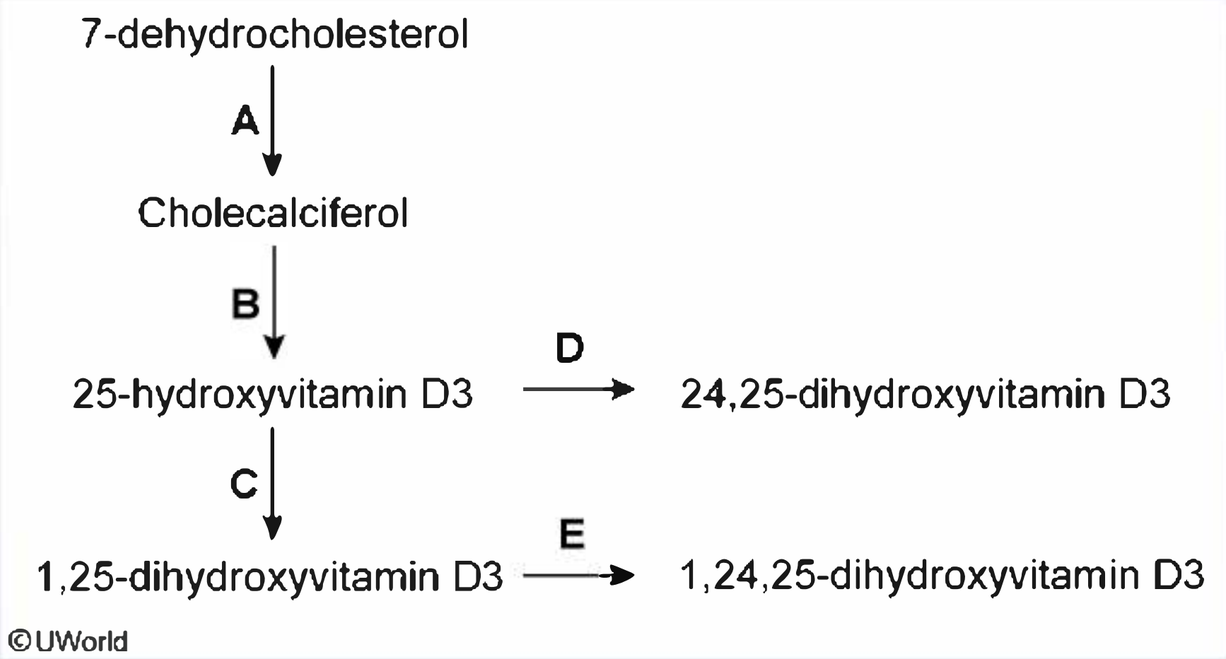
Educational objective:
Insulin has both renal and hepatic clearance. In patients with advanced chronic kidney disease and diabetes mellitus, decreased renal clearance of insulin can lead to symptomatic hypoglycemia if exogenous insulin doses are not adjusted based on the change in renal function.

References

- Pathophysiology and management of hypoglycemia in end-stage renal disease patients: a review.

Physiology Endocrine, Diabetes & Metabolism Diabetes mellitus

A 45-year-old man comes to the office due to "aching bones." He has a 2-month history of insidious-onset pain that is most pronounced in the back, pelvis, and lower extremities. The pain is dull and increases after weight-bearing activities. The patient has no prior medical conditions and takes no medications. He emigrated from Central Africa 5 years ago and works overnight shifts as a cab driver. Vital signs are within normal limits. Physical examination shows normal muscle strength in the upper and lower extremities bilaterally. A thorough laboratory evaluation establishes the diagnosis. After discussing the likely cause of his condition, the patient starts spending more time outdoors in the sun. Which of the following enzymatic steps will most likely be affected by this change in activity?



A. A
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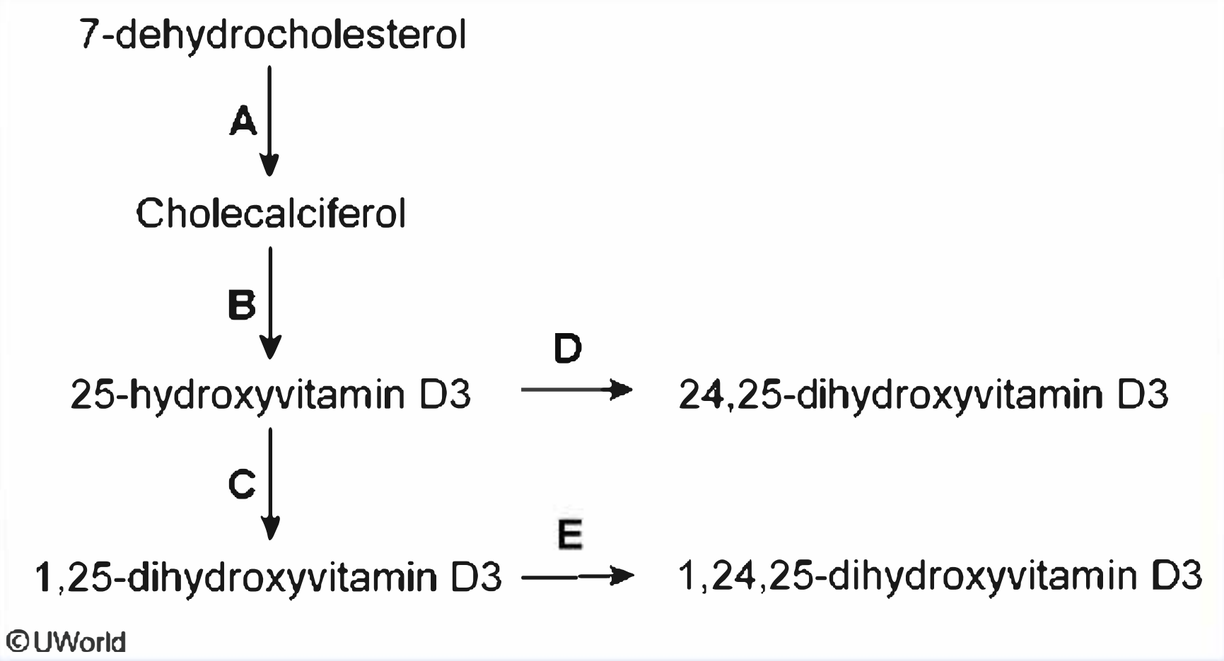

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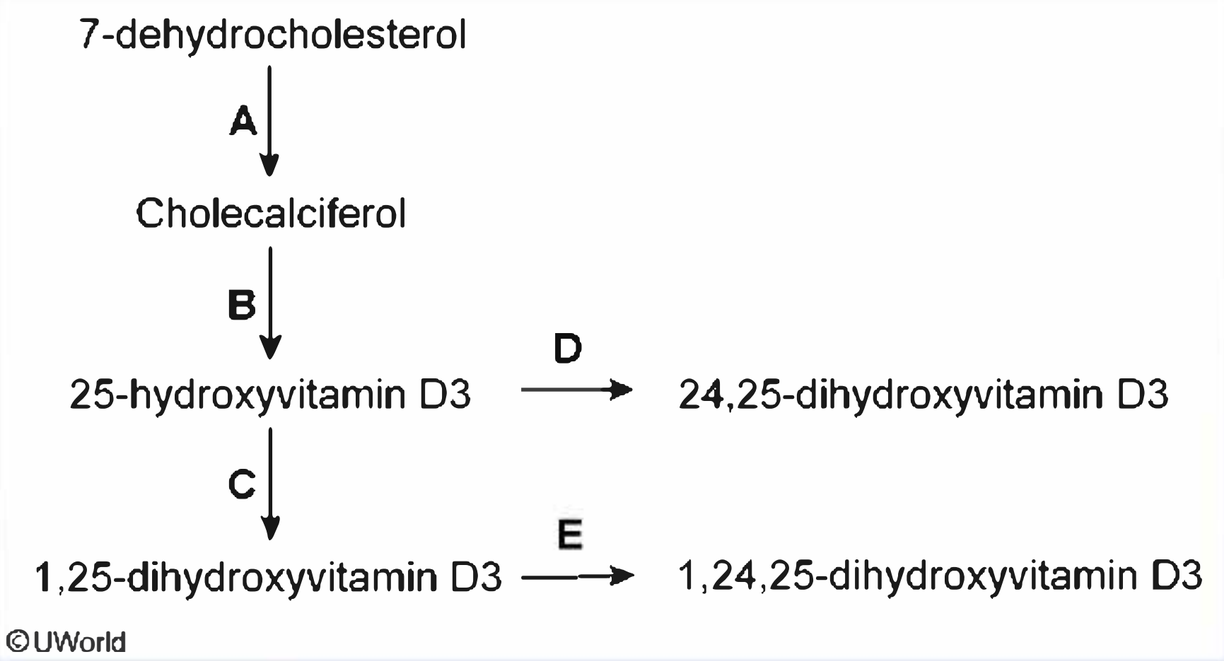

- A. A (63%)
- B. B (17%)
- C. C (13%)
- D. D (3%)
- E. E (1%)

Omitted
Correct answer

63%
Answered correctly

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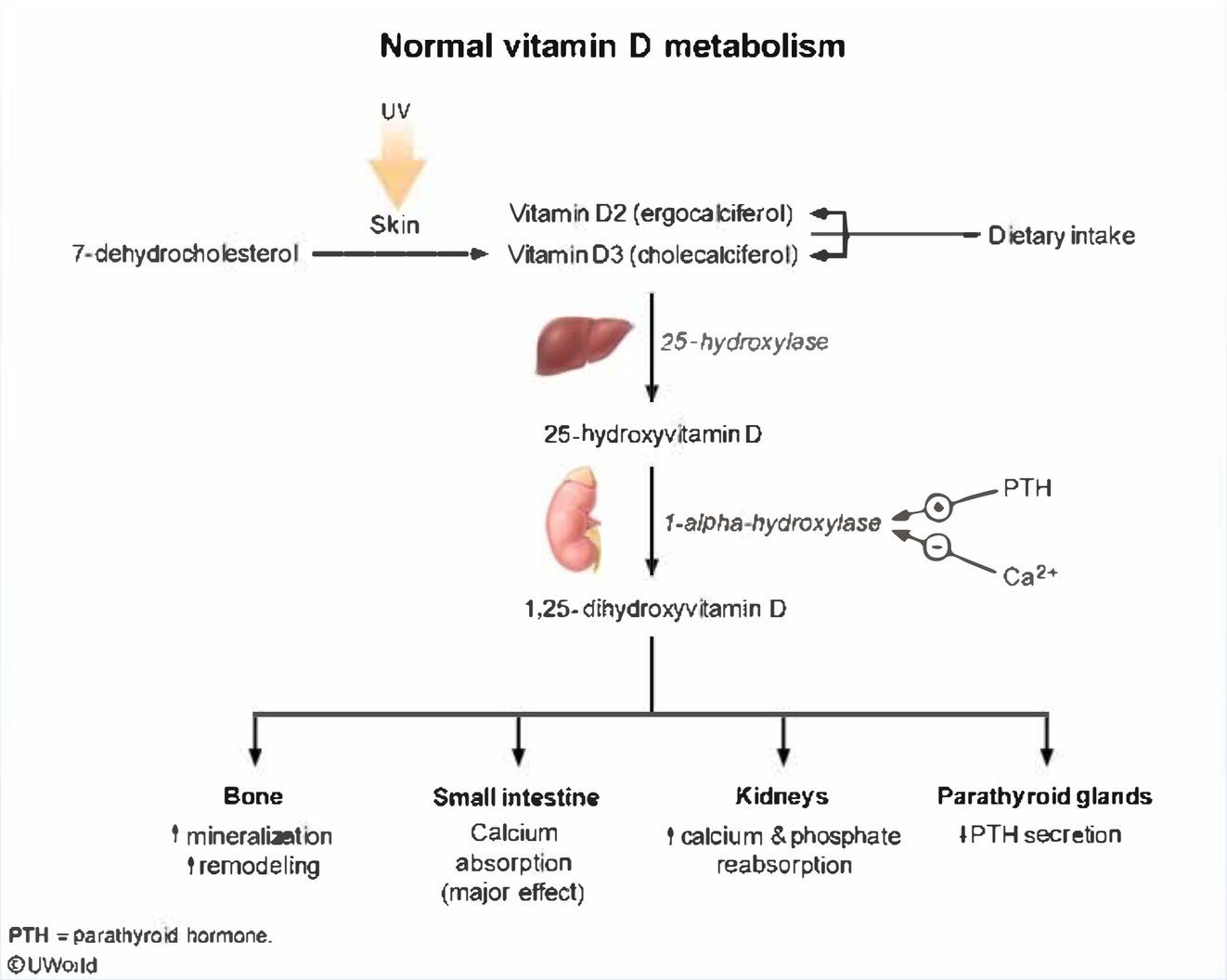

On exposure to **sunlight**, **7-dehydrocholesterol** (provitamin D3) in the skin absorbs ultraviolet (UV) B rays. This opens the B ring of 7-dehydrocholesterol, forming previtamin D3, which then undergoes thermal isomerization to form **vitamin D3** (cholecalciferol). Vitamin D3 is then

PTH = parathyroid hormone.

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Vitamin D deficiency can lead to osteomalacia with bone pain or tenderness, muscle weakness or cramps, gait abnormalities, and increased fracture risk. Factors associated with limited UV exposure and increased risk of vitamin D deficiency include the following:

- **Reduced time outdoors:** elderly individuals, patients living in residential care or who are frequently hospitalized, people who avoid going outdoors due to high risk of skin cancer
- **Low UV sun exposure:** individuals living at extreme northern or southern latitudes
- **Predominantly nocturnal lifestyle:** shift work or occupations requiring overnight work
- **Blockade of sunlight exposure:** people who use high-grade sunblock or wear full-coverage clothing
- **Reduced UV penetration:** individuals with heavily pigmented skin

(Choices B and C) The conversion of vitamin D2 and D3 to 25-hydroxycholecalciferol by 25-hydroxylase in the liver is primarily regulated by feedback inhibition from 25-hydroxycholecalciferol. The conversion to 1,25-dihydroxycholecalciferol by 1-alpha-hydroxylase in the kidney is primarily regulated by parathyroid hormone (PTH) and plasma calcium levels. Neither of these steps takes place in the skin or is affected by sunlight exposure.

(Choices D and E) 25-hydroxyvitamin D-24-hydroxylase converts 25- and 1,25-dihydroxyvitamin D into inactive 24-hydroxylated metabolites. It is upregulated by 1,25-dihydroxyvitamin D (to prevent excess vitamin D activity) and suppressed by parathyroid hormone (to facilitate replenishment of circulating calcium levels) and thus functions as a counterregulatory homeostatic enzyme. However, it is not affected by sunlight.

Educational objective:
Sunlight exposure catalyzes conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3) in the skin. Subsequent 25-hydroxylation in the liver and 1-hydroxylation in the kidneys produce 1,25-dihydroxyvitamin D, the active form. Inadequate exposure to sunlight can lead to vitamin D deficiency.

References

- **Reduced time outdoors:** elderly individuals, patients living in residential care or who are frequently hospitalized, people who avoid going outdoors due to high risk of skin cancer
- **Low UV sun exposure:** individuals living at extreme northern or southern latitudes
- **Predominantly nocturnal lifestyle:** shift work or occupations requiring overnight work
- **Blockade of sunlight exposure:** people who use high-grade sunblock or wear full-coverage clothing
- **Reduced UV penetration:** individuals with heavily pigmented skin

(Choices B and C) The conversion of vitamin D2 and D3 to 25-hydroxycholecalciferol by 25-hydroxylase in the liver is primarily regulated by feedback inhibition from 25-hydroxycholecalciferol. The conversion to 1,25-dihydroxycholecalciferol by 1-alpha-hydroxylase in the kidney is primarily regulated by parathyroid hormone (PTH) and plasma calcium levels. Neither of these steps takes place in the skin or is affected by sunlight exposure.

(Choices D and E) 25-hydroxyvitamin D-24-hydroxylase converts 25- and 1,25-dihydroxyvitamin D into inactive 24-hydroxylated metabolites. It is upregulated by 1,25-dihydroxyvitamin D (to prevent excess vitamin D activity) and suppressed by parathyroid hormone (to facilitate replenishment of circulating calcium levels) and thus functions as a counter-regulatory homeostatic enzyme. However, it is not affected by sunlight.

Educational objective:
Sunlight exposure catalyzes conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3) in the skin. Subsequent 25-hydroxylation in the liver and 1-hydroxylation in the kidneys produce 1,25-dihydroxyvitamin D, the active form. Inadequate exposure to sunlight can lead to vitamin D deficiency.

References

- Sunlight, ultraviolet radiation, vitamin D and skin cancer: how much sunlight do we need?

Physiology	Endocrine, Diabetes & Metabolism	Vitamin D deficiency
Subject	System	Topic

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A 26-year-old woman comes to the clinic due to worsening generalized weakness, myalgias, and unintentional weight loss. She has primary hypothyroidism for which she takes levothyroxine. Blood pressure is 110/70 mm Hg supine and 90/60 mm Hg standing. She appears mildly emaciated. Cardiopulmonary examination reveals no abnormalities. Laboratory studies show mild normochromic, normocytic anemia; eosinophil count of 15%; and serum glucose of 65 mg/dL. Which of the following additional changes is most likely in this patient?

	Serum Na	Serum K	Urine Na	Urine K
A.	↓	↑	↑	↓
B.	↓	Normal	↑	Normal
C.	↓	↓	↓	↑
D.	↓	↑	↓	↑
E.	Normal	↓	Normal	↑

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	Serum Na	Serum K	Urine Na	Urine K
✓ A. (55%)	↓	↑	↑	↓
B. (11%)	↓	Normal	↑	Normal
C. (13%)	↓	↓	↓	↑
D. (9%)	↓	↑	↓	↑
E. (10%)	Normal	↓	Normal	↑

Omitted
Correct answer
A

55%
Answered correctly

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Time Spent

06/09/2020
Last Updated

Explanation

This patient has multiple clinical features that suggest **primary adrenal insufficiency** (PAI) (also known as Addison disease). PAI most

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This patient has multiple clinical features that suggest **primary adrenal insufficiency** (PAI) (also known as Addison disease). PAI most commonly results from autoimmune destruction of the bilateral adrenal cortex and often occurs in patients with a preexisting history of **autoimmune disease** (eg, hypothyroidism, type 1 diabetes mellitus). Reduced mineralocorticoid (mainly aldosterone) production leads to renal salt wasting with consequent **hypovolemia and orthostasis** (systolic blood pressure decrease ≥20 mm Hg with standing). Reduced cortisol can lead to **hypoglycemia**, normocytic **anemia**, and **eosinophilia**.

In the renal collecting tubule principal cells, reduced aldosterone leads to markedly decreased sodium absorption and increased potassium absorption; therefore, there is **high urine sodium** and **low urine potassium**. Serum potassium is elevated **(hyperkalemia)** due to the increased tubular absorption. Although the tubular salt wasting reduces total body sodium, it does not directly affect serum sodium concentration. However, because hypovolemia provides nonosmotic stimulus for antidiuretic hormone (ADH) secretion and ADH secretion is normally inhibited by cortisol, ADH levels are increased in PAI. The increased ADH levels lead to increased water retention and low serum sodium **(hyponatremia)**.

(Choice B) Hyponatremia in the setting of high urine sodium is characteristic of the syndrome of inappropriate ADH secretion (SIADH). SIADH has no significant effect on serum and urine potassium levels.

(Choices C and D) In hypovolemic states (eg, severe vomiting, diabetic ketoacidosis), restoration of blood volume is the highest priority. Therefore, the kidneys respond by stimulating increased aldosterone secretion, which decreases urine sodium and increases urine potassium. The hypovolemia also provides nonosmotic stimulus for ADH release, which leads to hyponatremia. Both total body and serum potassium are low in severe vomiting due to both gastrointestinal and renal losses. Although total body potassium is low in diabetic ketoacidosis, serum potassium is high because potassium is unable to enter cells in the absence of insulin.

(Choice E) Primary hyperaldosteronism causes potassium wasting by the renal principal cells, leading to high urine potassium and low serum potassium (hypokalemia). There is renal sodium retention that leads to increased blood volume, but any significant change in serum or urine sodium concentration is avoided due to aldosterone escape.

Educational objective:
Reduced aldosterone production in primary adrenal insufficiency leads to renal sodium wasting with consequent hypovolemia, orthostasis, and potassium retention (hyperkalemia). Low cortisol stimulates increased antidiuretic hormone secretion, which leads to water retention and hyponatremia.

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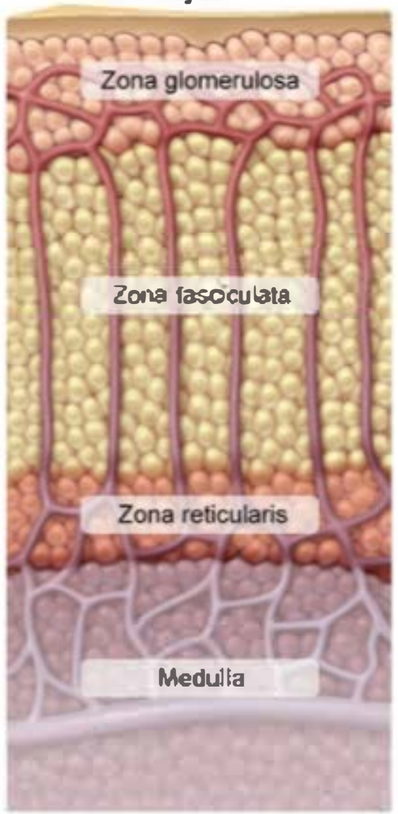
Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		



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Educational objective:
Reduced aldosterone production in primary adrenal insufficiency leads to renal sodium wasting with consequent hypovolemia, orthostasis, and potassium retention (hyperkalemia). Low cortisol stimulates increased antidiuretic hormone secretion, which leads to water retention and hyponatremia.

Physiology	Endocrine, Diabetes & Metabolism	Adrenal insufficiency
Subject	System	Topic

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A group of researchers is developing new drugs for osteoporosis. They are testing a new drug, Substance X, that exhibits the following metabolic effects when given via an infusion in varying doses (as shown in the graphs below).

Which of the following most closely resembles the metabolic effects of Substance X?

A. 1,25-dihydroxyvitamin D analog

B. Fibroblast growth factor 23 inhibitor

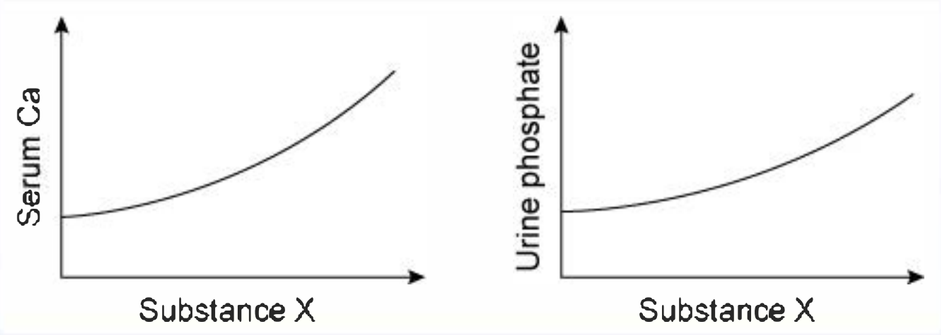
C. Pyrophosphate analog

D. Receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor

E. Recombinant parathyroid hormone

Submit

A group of researchers is developing new drugs for osteoporosis. They are testing a new drug, Substance X, that exhibits the following metabolic effects when given via an infusion in varying doses (as shown in the graphs below).



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C. Pyrophosphate analog

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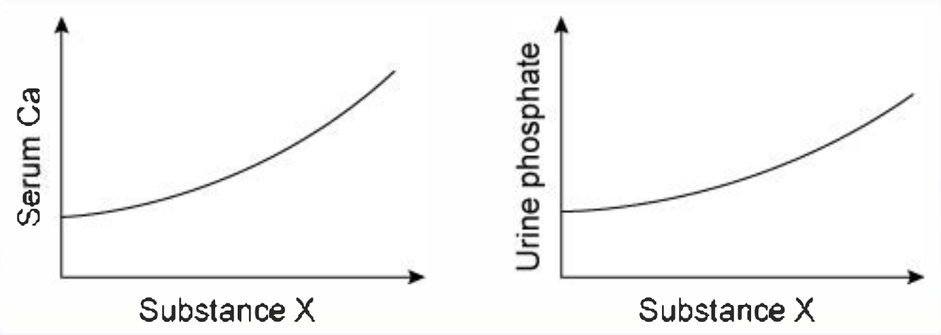

Which of the following most closely resembles the metabolic effects of Substance X?

A. 1,25-dihydroxyvitamin D analog (12%)

B. Fibroblast growth factor 23 inhibitor (0%)

C. Pyrophosphate analog (0%)

D. Receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor (1%)

E. Recombinant parathyroid hormone (83%)

Omitted
Correct answer
E

83%
Answered correctly

03 secs
Time Spent

03/15/2020
Last Updated

Explanation

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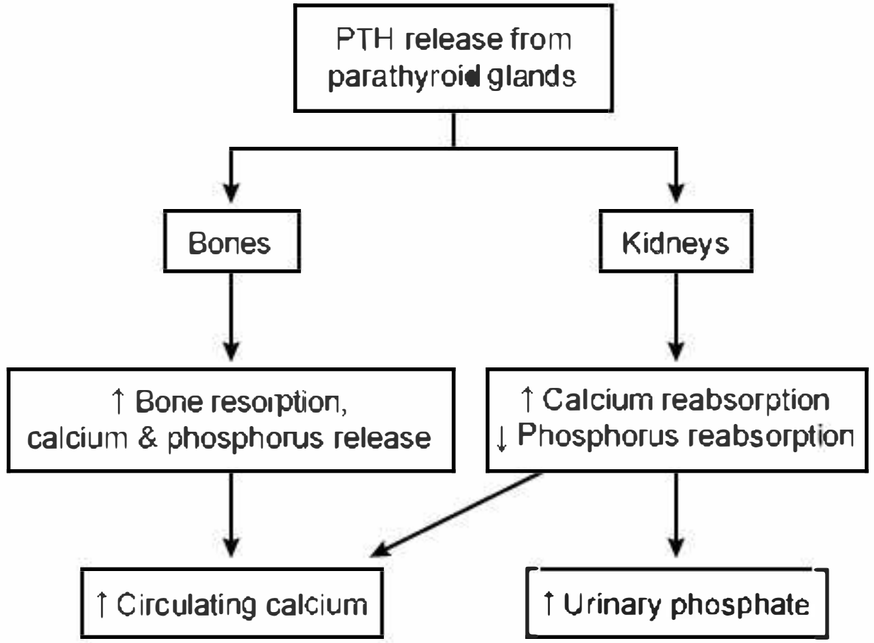
Parathyroid hormone, calcium, and phosphorus



PTH = parathyroid hormone.

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This investigational drug causes a dose-dependent increase in serum calcium and urine phosphate excretion, which resembles the activity of **parathyroid hormone** (PTH).

PTH receptors are located on osteoblasts (not osteoclasts), and activation causes osteoblasts to increase production of receptor activator of nuclear factor kappa-B ligand (RANK-L) and monocyte colony-stimulating factor. These factors stimulate osteoclastic precursors to differentiate into bone-resorbing osteoclasts. PTH also decreases the release of osteoprotegerin (OPG), a decoy receptor for RANK-L; therefore, lower levels

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Chronically high levels of PTH (ie, hyperparathyroidism) increase the risk of osteoporosis. However, intermittent administration of recombinant PTH analogs induces a greater increase in osteoblast activity in proportion to osteoclast activity and a net increase in new bone formation. Teriparatide is a recombinant PTH analog used to treat osteoporosis.

(Choice A) PTH increases renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which increases intestinal absorption of calcium and phosphate and decreases PTH secretion via negative feedback. 1,25-dihydroxyvitamin D analogs (eg, calcipotriol) can raise serum calcium to some extent, but suppression of PTH limits the degree of phosphate excretion in the urine.

(Choice B) PTH increases renal phosphate excretion by inducing internalization and destruction of type IIa sodium/phosphate cotransporters (NPT2) in the proximal renal tubule. Fibroblast growth factor 23 (FGF23) is a hormone produced by osteocytes that acts synergistically with PTH to increase phosphate excretion by downregulating NPT2 gene expression. Investigational FGF23 inhibitors reduce renal phosphate excretion.

(Choices C and D) Bisphosphonates (eg, alendronate, risedronate) are pyrophosphate analogs that attach to hydroxyapatite binding sites on bone surfaces and inhibit osteoclast-mediated bone resorption. Denosumab is a monoclonal antibody that decreases bone resorption by binding to RANK-L and blocking the interaction between RANK-L and RANK on osteoclast surfaces. These agents generally lower, rather than raise, serum calcium levels.

Educational objective:
Parathyroid hormone (PTH) causes increased bone resorption, increased serum calcium levels, and increased renal phosphate excretion. Chronically high levels of PTH increase the risk of osteoporosis. However, intermittent administration of recombinant PTH analogs (eg,

of OPG allow for more interaction between RANK-L and the osteoclastic receptor, **increasing bone resorption** and **releasing calcium and phosphate** into circulation. In the kidney, PTH **decreases tubular reabsorption of phosphorus** while increasing reabsorption of calcium. Therefore, the combined effects are **increased serum calcium** and **urine phosphate levels**.

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Parathyroid hormone (PTH) causes increased bone resorption, increased serum calcium levels, and increased renal phosphate excretion. Chronically high levels of PTH increase the risk of osteoporosis. However, intermittent administration of recombinant PTH analogs (eg, teriparatide) induces a greater increase in osteoblast activity in proportion to osteoclast activity and a net increase in bone formation.

Physiology	Endocrine, Diabetes & Metabolism	Hypercalcemia
Subject	System	Topic

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A collection of tan fat-containing tissue is found around the kidneys and adrenal glands of a newborn during surgery. Surgical removal of the tissue would most likely contribute to:

A. Fasting hypoglycemia

B. Hypercholesterolemia

C. Fasting ketonemia

D. Lactic acidosis

E. Hypothermia

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A collection of tan fat-containing tissue is found around the kidneys and adrenal glands of a newborn during surgery. Surgical removal of the tissue would most likely contribute to:

A. Fasting hypoglycemia (14%)

B. Hypercholesterolemia (4%)

C. Fasting ketonemia (3%)

D. Lactic acidosis (3%)

✓ E. Hypothermia (74%)

Omitted
Correct answer
E

74%
Answered correctly

05 secs
Time Spent

02/03/2020
Last Updated

Explanation

Brown adipose tissue comprises 5% of body mass in neonates. It is also found in hibernating animals, but is present in very small amounts in adult humans. The main function of brown adipose tissue is heat production (**Choice E**). Neonates have many physiological traits that make them more susceptible to hypothermia, such as an immature nervous system, a high body surface area to volume ratio and a decreased ability to shiver for heat production. Heat production by brown adipose tissue is, therefore, necessary for neonatal survival.

White adipose tissue is composed of cells that contain one intracytoplasmic fat droplet. Unlike white adipocytes, brown adipocytes possess several small intracytoplasmic fat vacuoles and considerably more mitochondria. The drastically increased number of mitochondria in these cells gives brown adipose tissue its tan color. Brown adipose tissue has a higher oxygen requirement and contains more capillaries than white adipose

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In the majority of human cells, mitochondria are the sites of ATP production. In the mitochondria of brown adipose tissue electron transport and phosphorylation are uncoupled. The protons pumped out by electron transport chain return to the matrix via the mitochondrial membrane protein thermogenin, also known as an uncoupling protein. Thus no ATP is synthesized, and the energy released by electron transport is dissipated as heat.

(Choice A) A defect in gluconeogenesis or glycogenolysis would lead to fasting hypoglycemia. These processes primarily occur in the liver.

(Choice B) Hypercholesterolemia is most commonly due to a genetic / familial predisposition for high serum cholesterol levels. It may also be induced by diets high in cholesterol.

(Choice C) Ketonemia occurs when the liver is depleted of glycogen and utilizes body fat for gluconeogenesis. It occurs during sleep, fasting, starvation, and due to metabolic disturbances in diabetes mellitus.

(Choice D) Lactic acidosis results in states of tissue hypoxia or in the presence of defects in oxidative phosphorylation because pyruvate generated by glycolysis is converted to lactate rather than acetyl-CoA in these states.

Educational Objective:
Brown adipose tissue is found in newborns and in hibernating mammals. Brown adipose cells contain several intracytoplasmic fat droplets and many more mitochondria than white adipose cells. They function to produce heat by uncoupling oxidative phosphorylation with the protein thermogenin.

White adipose tissue is composed of cells that contain one intracytoplasmic fat droplet. Unlike white adipocytes, brown adipocytes possess several small intracytoplasmic fat vacuoles and considerably more mitochondria. The drastically increased number of mitochondria in these cells gives brown adipose tissue its tan color. Brown adipose tissue has a higher oxygen requirement and contains more capillaries than white adipose tissue.

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Educational Objective:
Brown adipose tissue is found in newborns and in hibernating mammals. Brown adipose cells contain several intracytoplasmic fat droplets and many more mitochondria than white adipose cells. They function to produce heat by uncoupling oxidative phosphorylation with the protein thermogenin.

Physiology	Endocrine, Diabetes & Metabolism	Oxidative phosphorylation
Subject	System	Topic

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Researchers studying the pathophysiology of diabetes mellitus identify a family with an inherited mutation in the insulin gene. The mutation results in a single amino acid substitution in the proinsulin molecule. However, affected family members are asymptomatic, and most have completely normal blood glucose levels. Analysis of the mature insulin molecule shows that it is identical to normal human insulin. The researchers conclude that the amino acid substitution affects a segment of proinsulin removed during post-translational processing of the protein. The polypeptide segment containing the mutation is most likely to undergo which of the following processes within pancreatic beta cells?

A. Degradation in lysosomes

B. Degradation in proteasomes

C. Degradation in the rough endoplasmic reticulum

D. Direct translocation across the plasma membrane

E. Storage in secretory granules

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Researchers studying the pathophysiology of diabetes mellitus identify a family with an inherited mutation in the insulin gene. The mutation results in a single amino acid substitution in the proinsulin molecule. However, affected family members are asymptomatic, and most have completely normal blood glucose levels. Analysis of the mature insulin molecule shows that it is identical to normal human insulin. The researchers conclude that the amino acid substitution affects a segment of proinsulin removed during post-translational processing of the protein. The polypeptide segment containing the mutation is most likely to undergo which of the following processes within pancreatic beta cells?

A. Degradation in lysosomes (9%)

B. Degradation in proteasomes (30%)

C. Degradation in the rough endoplasmic reticulum (8%)

D. Direct translocation across the plasma membrane (13%)

✓ E. Storage in secretory granules (39%)

Omitted
Correct answer
E

39%
Answered correctly

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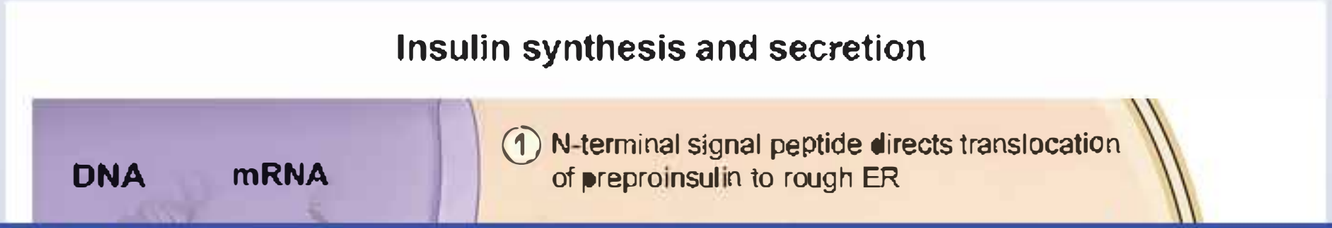
Time Spent

05/07/2020
Last Updated

Explanation



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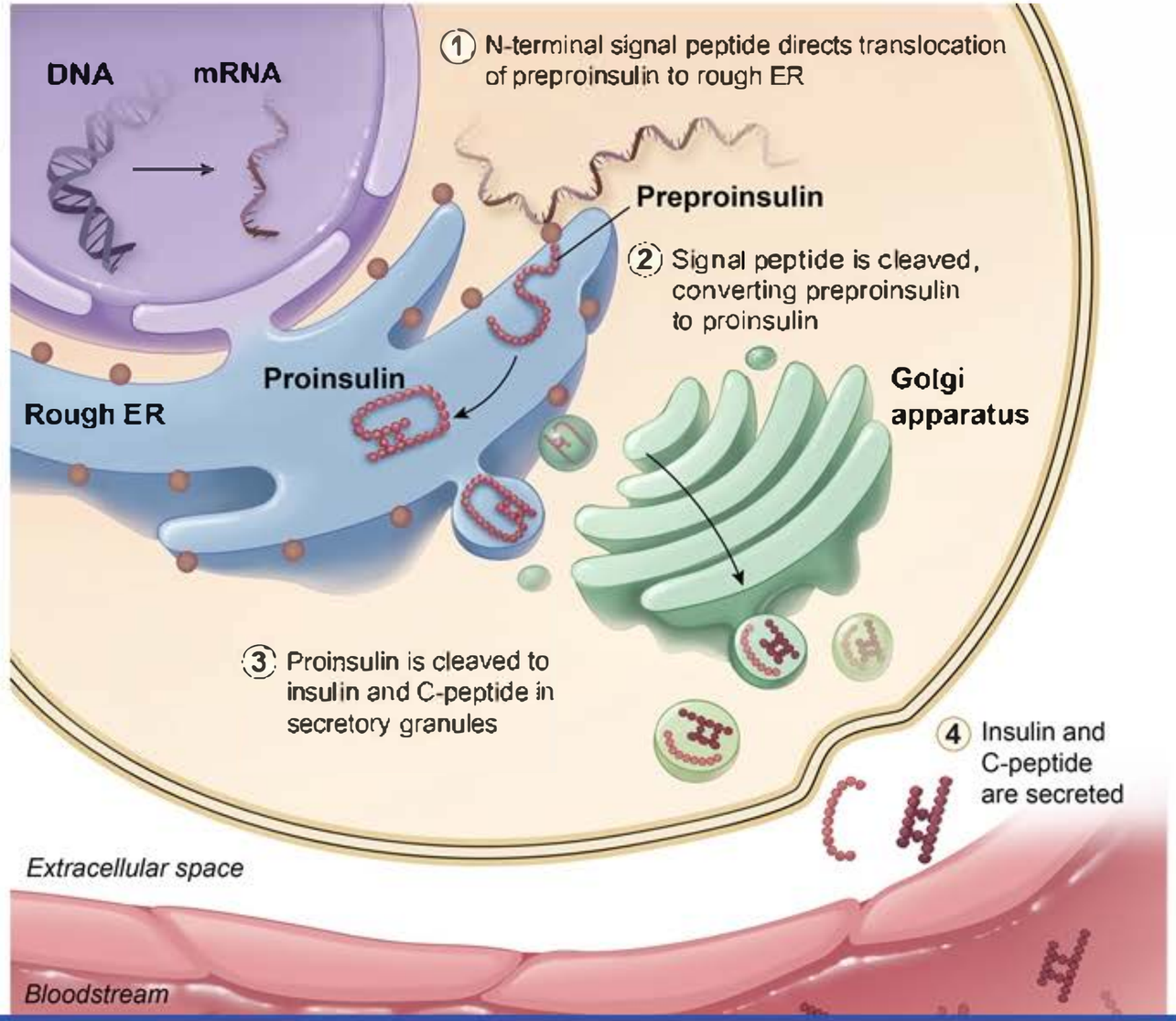
Insulin synthesis and secretion



©UWorld ER = endoplasmic reticulum.

Insulin, a polypeptide hormone synthesized by pancreatic beta cells, is released in response to elevated glucose levels. Insulin mRNA codes for **preproinsulin**, a larger precursor molecule that begins with a hydrophobic N-terminal signal peptide. Shortly after translation begins, this signal sequence interacts with cytosolic signal recognition peptide, which halts protein synthesis until the ribosome translocates to the rough endoplasmic reticulum (RER). Once bound to the RER, translation resumes and the growing peptide chain is extruded into the RER. The N-terminal signal peptide is then cleaved from preproinsulin to yield **proinsulin**.

Proinsulin undergoes conformational changes and the addition of 3 disulfide bonds in the RER. Proinsulin is then transported to the Golgi apparatus, where it is packed into secretory granules. Endopeptidases in the secretory granules cleave proinsulin into **insulin** and **C-peptide**, which are then stored within the granules until they are secreted from the cell via exocytosis **(Choices A, B, and C)**.

Exogenous insulin administered to patients with diabetes does not contain C-peptide. However, C-peptide released from beta cells remains in the circulation with a half-life of approximately 35 minutes and can be assayed as a surrogate marker for endogenous insulin production.

(Choice D) Most proteins destined for the extracellular space have a signaling sequence that directs them to the RER/Golgi apparatus, where they are packaged into secretory vesicles. However, a few proteins, such as interleukin-1, lack a signaling sequence and are secreted directly from the cytoplasm via an unconventional mechanism.

Educational objective:
Cleavage of proinsulin in pancreatic beta-cell secretory granules yields insulin and C-peptide, which are stored in the granules until they are secreted in equimolar amounts.

References

- Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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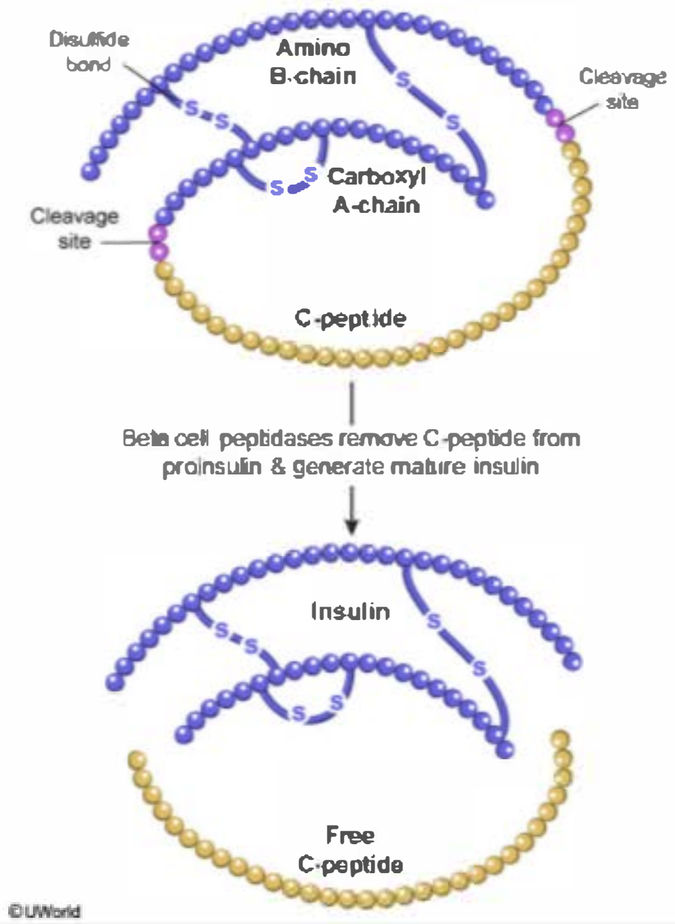
Exhibit Display

Proinsulin to insulin



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A 4-week-old infant is evaluated for frequent episodes of hypoglycemia. The patient is found to have elevated insulin levels during periods of fasting. Several members of his family have a similar condition. Genetic testing reveals a mutation involving potassium channels expressed in pancreatic beta cells. The mutated channels have a higher sensitivity to the substance that normally modulates their activity, causing increased beta cell secretory activity. Which of the following substances normally binds to and regulates the ion channels that are responsible for this patient's hypoglycemia?

A. ATP
B. Citrate
C. Fructose-6-phosphate
D. Fumarate
E. Glucose
F. Lactate
G. Malate
H. Pyruvate

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- ✓ A. ATP (68%)
- B. Citrate (2%)
- C. Fructose-6-phosphate (3%)
- D. Fumarate (0%)
- E. Glucose (22%)
- F. Lactate (0%)
- G. Malate (0%)
- H. Pyruvate (1%)

Omitted
Correct answer
A

68%
Answered correctly

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06/07/2020
Last Updated

Explanation

Pancreatic beta cell function

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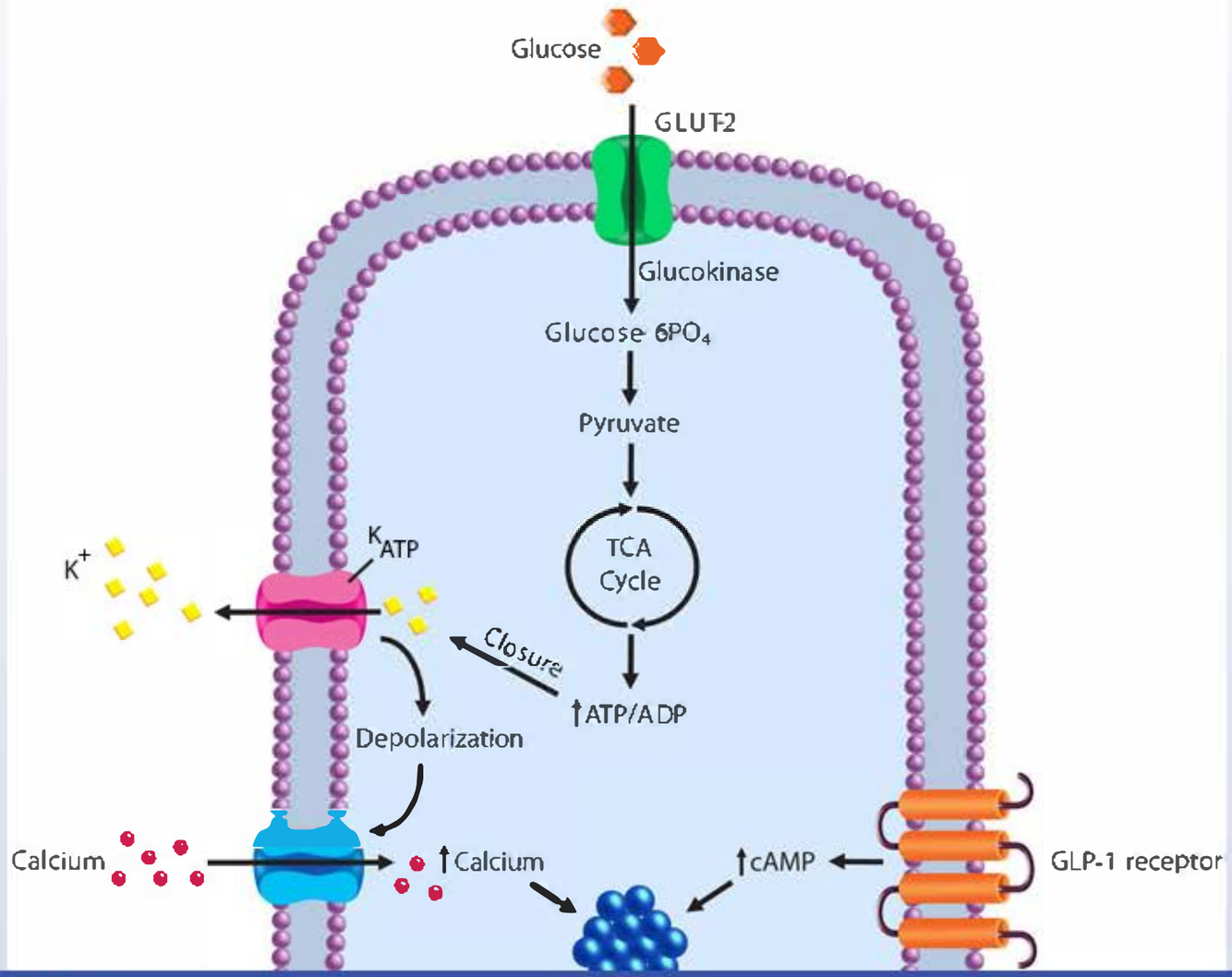
Pancreatic beta cell function



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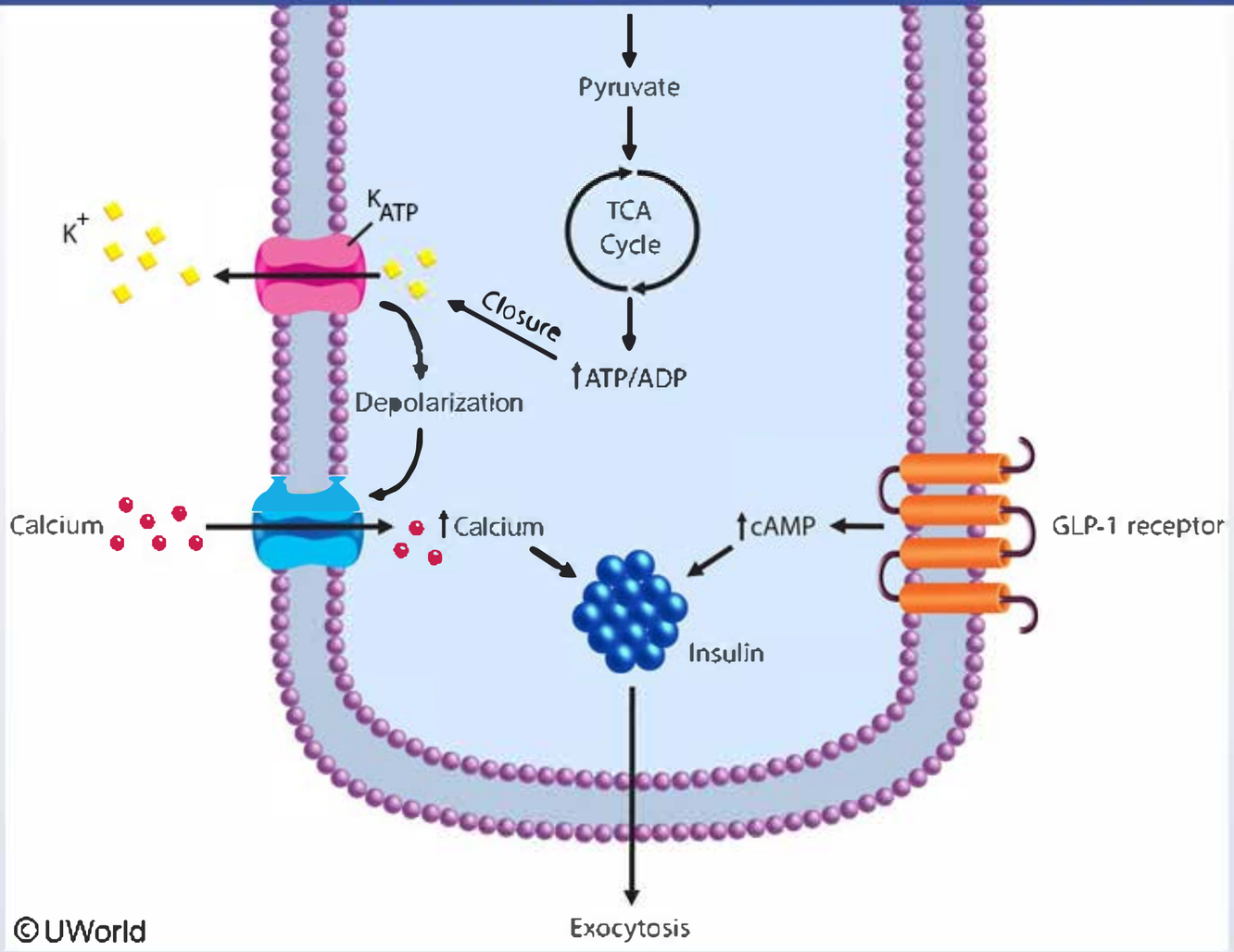

Pancreatic beta cells secrete insulin in response to elevated **glucose** levels. Glucose enters beta cells via **glucose transporter 2** (GLUT-2) and is metabolized via glycolysis and the citric acid cycle to generate **ATP**. ATP then binds to the regulatory subunit of the **ATP-sensitive potassium channel** (K_{ATP} channel). K_{ATP} channels are normally open at rest and maintain membrane polarization by allowing outward movement of potassium from the beta cells; however, on binding ATP, the K_{ATP} channels close. Increased intracellular ATP therefore leads to decreased

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Exocytosis

Pancreatic beta cells secrete insulin in response to elevated **glucose** levels. Glucose enters beta cells via **glucose transporter 2** (GLUT-2) and is metabolized via glycolysis and the citric acid cycle to generate **ATP**. ATP then binds to the regulatory subunit of the **ATP-sensitive potassium channel** (K_{ATP} channel). K_{ATP} channels are normally open at rest and maintain membrane polarization by allowing outward movement of potassium from the beta cells; however, on binding ATP, the K_{ATP} channels close. Increased intracellular ATP therefore leads to decreased potassium efflux and **membrane depolarization**. This triggers opening of voltage-dependent calcium channels, increased intracellular calcium levels, and subsequent **insulin release**.

Mutations in the K_{ATP} channel causing increased affinity for ATP result in fewer open channels and depolarization at lower glucose concentrations. This causes continued secretion of insulin despite falling blood glucose levels, leading to congenital hypoglycemia. Conversely, mutations of the K_{ATP} channels that decrease ATP affinity prevent appropriate depolarization in response to rising glucose levels, causing a familial form of neonatal diabetes mellitus. These patients can be treated successfully with sulfonylureas, which bind to K_{ATP} channels and cause closure independent of ATP.

(Choices B, D, and G) Citrate, fumarate, and malate are intermediate products in the citric acid cycle. During this process, energy is stored as NADH and $FADH_2$. ATP is then produced when NADH and $FADH_2$ enter oxidative phosphorylation. However, these intermediates do not directly interact with K_{ATP} channels.

(Choices C, F, and H) Fructose-6-phosphate and pyruvate are products of the glycolytic pathway. Lactate is produced from pyruvate during anaerobic glycolysis. Glycolysis raises intracellular ATP levels, but these glycolytic intermediates do not act on K_{ATP} channels directly.

(Choice E) Glucose induces insulin release from beta cells via ATP formation but does not interact with K_{ATP} channels directly.

Educational objective:
Oxidative metabolism of glucose in pancreatic beta cells generates ATP. ATP-induced closure of the ATP-sensitive potassium channels leads to membrane depolarization and subsequent insulin release.

References

- Hyperinsulinemic hypoglycemia

Physiology Endocrine Diseases & Metabolism Hypoglycemia

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A 23-year-old healthy man who lives at sea level is attempting to trek to the Mount Everest base camp at an elevation of 5,334 m (17,500 ft). While hiking, he experiences mild shortness of breath, lightheadedness, headache, and fatigue. The patient reaches the base camp after 7 days, where he is evaluated at a high-altitude clinic. He appears exhausted, but physical examination is otherwise unrevealing. Which of the following physiologic changes has most likely occurred in this patient?

A. Decreased peripheral chemoreceptor firing

B. Decreased pulmonary vascular resistance

C. Decreased renal erythropoietin production

D. Increased erythrocyte 2,3-bisphosphoglycerate (2,3-BPG) synthesis

E. Increased renal HCO_3^- reabsorption

Submit

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A. Decreased peripheral chemoreceptor firing (4%)

B. Decreased pulmonary vascular resistance (3%)

C. Decreased renal erythropoietin production (1%)

✓ D. Increased erythrocyte 2,3-bisphosphoglycerate (2,3-BPG) synthesis (81%)

E. Increased renal HCO_3^- reabsorption (9%)

Omitted
Correct answer
D

81%
Answered correctly

02 secs
Time Spent

04/26/2020
Last Updated

Explanation

High-altitude illness	
Pathogenesis	• Reduced PiO_2 at high altitude (>2,500 m [~8000 ft])
Physiologic responses	• Hyperventilation: helps ↑ PaO_2 but causes ↓ $PaCO_2$ • Erythrocytes: ↑ 2,3-BPG production (↑ O_2 unloading in tissues)

High-altitude illness	
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Physiologic responses	• Hyperventilation: helps ↑ PaO_2 but causes ↓ $PaCO_2$ • Erythrocytes: ↑ 2,3-BPG production (↑ O_2 unloading in tissues) • Kidneys: ↑ Erythropoietin production & ↑ HCO_3^- excretion

Complications	• Acute mountain sickness
	  ∘ Headache, fatigue, nausea
	• Cerebral edema (↓ PaO_2 → ↑ cerebral blood flow)
	  ∘ Lethargy, confusion, gait disturbance
	• Pulmonary edema (unbalanced hypoxic vasoconstriction)
	  ∘ Dyspnea, cough ± hemoptysis, respiratory distress

2,3-BPG = 2,3-bisphosphoglycerate; PiO_2 = partial pressure of inspired oxygen.

This patient is most likely suffering from **acute mountain sickness (AMS)**, a type of **high-altitude illness** resulting from low partial pressure of oxygen (pO_2) in environments >2,500 m (8,000 ft). Although the fraction of oxygen in inspired air remains constant (21%) at different terrestrial elevations, barometric pressure drops with increasing altitude, leading to decreased pO_2 in the air and lungs.

In an otherwise healthy patient, the pO_2 rapidly equilibrates between the alveoli and arterial blood, causing **hypoxemia** when the pO_2 drops below 80 mm Hg. Several acute physiological changes occur in response to the resulting **hypobaric hypoxia**:

- Increased firing of peripheral chemoreceptors causes hyperventilation, which directly reduces hypoxemia and improves tissue oxygenation **(Choice A)**.
- **Increased 2,3-bisphosphoglycerate (2,3-BPG)** synthesis by erythrocytes, which shifts the O_2-hemoglobin dissociation curve to the right, decreasing the affinity of hemoglobin for oxygen and facilitating the offloading of oxygen in peripheral tissues.

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Hyperventilation also decreases the partial pressure of carbon dioxide, resulting in increased blood pH (**respiratory alkalosis**). Common symptoms of AMS include headache, fatigue, dyspnea, dizziness, and sleep disturbances. Most cases subside within 2 days but can progress to life-threatening cerebral and/or pulmonary edema in susceptible patients. In the absence of underlying pathology, symptoms typically resolve within 48 hours as the kidneys **increase HCO_3^- excretion** to compensate for the alkalosis, restoring pH toward the normal range and improving symptoms **(Choice E)**.

(Choice B) Hypoxia induces widespread vasoconstriction of the pulmonary vasculature; this increases pulmonary vascular resistance and pulmonary arterial pressure and can result in pulmonary edema.

(Choice C) Hypoxemia stimulates increased erythropoietin production in the renal cortex, which results in polycythemia and increased oxygen-carrying capacity over time (days to weeks of sustained hypoxemia).

Educational objective:
People traveling to elevations >2500 m (8000 ft) can develop high-altitude illness, characterized by hypobaric hypoxia with the potential to develop life-threatening cerebral and/or pulmonary edema. Key adaptive responses to hypoxemia include hyperventilation to increase blood oxygenation and increased synthesis of 2,3-bisphosphoglycerate in erythrocytes (facilitating oxygen offloading into peripheral tissues).

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Physiology	General Principles	High altitude illness
Subject	System	Topic

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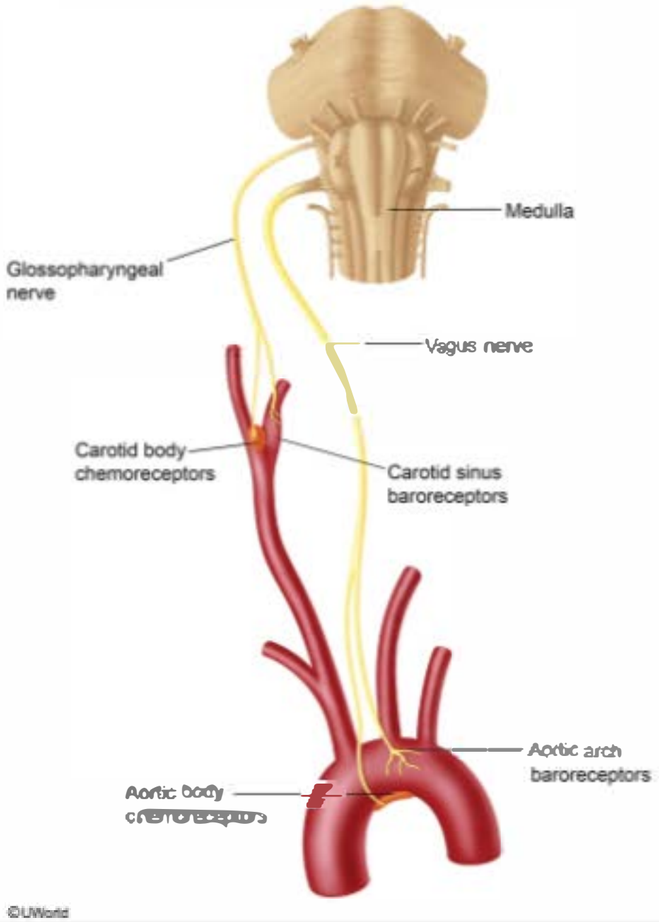

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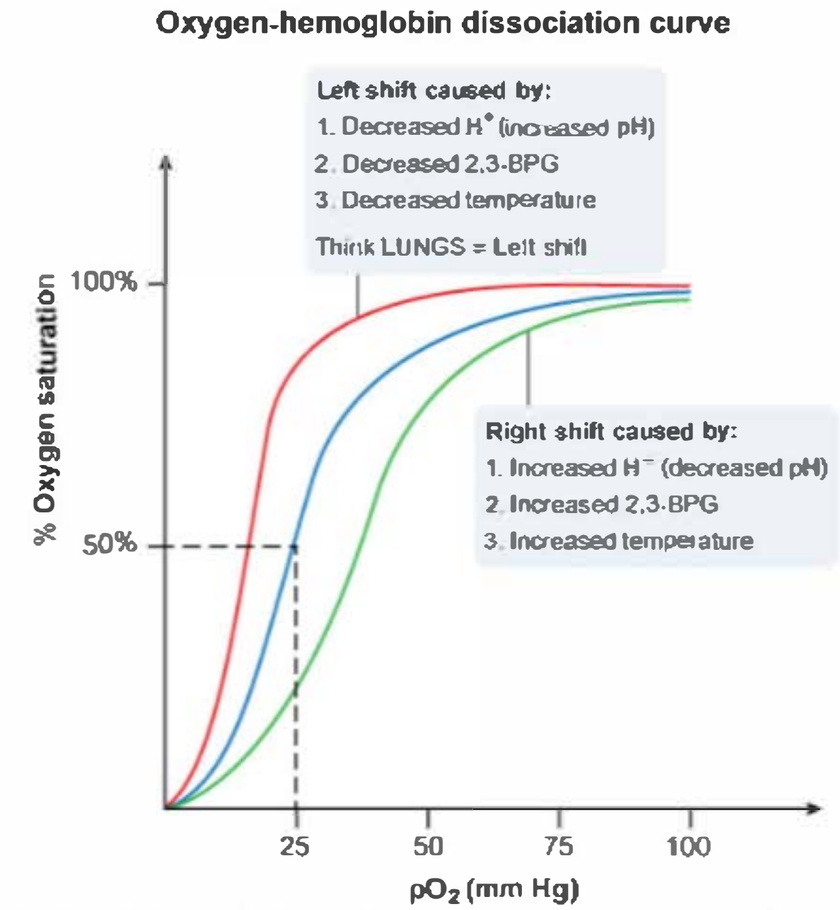

2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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A 46-year-old man develops episodes of "dizzy spells" accompanied by palpitations and sweating during exercise. His symptoms improve after drinking orange juice or eating a protein bar. The patient was diagnosed with type 2 diabetes 6 months ago and advised to lose weight with dietary modification and exercise. Since then, he has been working out intensively and has lost 10 kg (22 lb). Which of the following mechanisms is responsible for this patient's symptoms when exercising?

A. Decreased hepatic glucose production

B. Increased glucokinase activity

C. Increased glucose-6-phosphatase activity

D. Translocation of glucose transporter 2 to the cell membrane

E. Translocation of glucose transporter 4 to the cell membrane

Submit

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- A. Decreased hepatic glucose production (20%)
- B. Increased glucokinase activity (8%)
- C. Increased glucose-6-phosphatase activity (6%)
- D. Translocation of glucose transporter 2 to the cell membrane (6%)
- ✓ E. Translocation of glucose transporter 4 to the cell membrane (57%)

Omitted
Correct answer
E

57%
Answered correctly

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Time Spent

07/01/2020
Last Updated

Explanation

Glucose uptake in skeletal muscle occurs by facilitated diffusion via **glucose transporter (GLUT) 4**. In the fed state, **insulin** induces muscular glucose uptake by stimulating translocation of GLUT4 from intracellular depots to the plasma membrane and T tubules. As circulating glucose and insulin levels fall in the fasting state, GLUT4 is resequestered, and muscle becomes increasingly dependent on internal stores of glucose and glycogen and, subsequently, on fatty acids released by lipolysis in the liver.

However, **translocation of GLUT4** is also induced by **muscle contraction**, allowing insulin-independent **glucose uptake during exercise**. Over time, regular exercise also causes increased expression of GLUT4 and greater insulin-dependent GLUT4 translocation, leading to increased

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This patient has been engaging in a regular exercise program and is likely experiencing rapid uptake of glucose while exercising. As blood glucose levels fall, counterregulatory factors (eg, glucagon, epinephrine) are activated, leading to his symptoms (eg, palpitations, sweating), which are then relieved by the intake of sugar. **Exercise-induced hypoglycemia** is common in patients with diabetes mellitus due to the lack of physiologic insulin regulation along with insufficient carbohydrate supplementation.

(Choice A) As blood glucose levels fall during fasting or exercise, glucagon and epinephrine stimulate hepatic glycogenolysis and gluconeogenesis, leading to increased (not decreased) glucose production.

(Choice B) Glucokinase phosphorylates glucose to glucose 6-phosphate, primarily for glycogen synthesis. It is expressed mainly in the liver and is stimulated by rising, not falling, glucose levels.

(Choice C) Glucose 6-phosphatase catalyzes the hydrolysis of glucose 6-phosphate to glucose during gluconeogenesis, thereby helping to maintain glucose levels in the fasting state; increased activity would improve hypoglycemic symptoms by increasing circulating glucose levels.

(Choice D) GLUT2 is found primarily in the liver and pancreatic beta cells, where it facilitates insulin-independent glucose uptake. It is not expressed significantly in muscle or translocated in response to muscle contraction.

Educational objective:
Glucose uptake in skeletal muscle occurs primarily via glucose transporter (GLUT) 4. Muscle contraction and insulin induce translocation of GLUT4 to the cell surface, increasing glucose uptake during exercise and the fed state, respectively. Over time, regular exercise causes increased expression of GLUT4, leading to increased skeletal muscle glucose uptake at any given insulin level and therefore lower blood glucose levels.

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References

- Exercise, GLUT4, and skeletal muscle glucose uptake.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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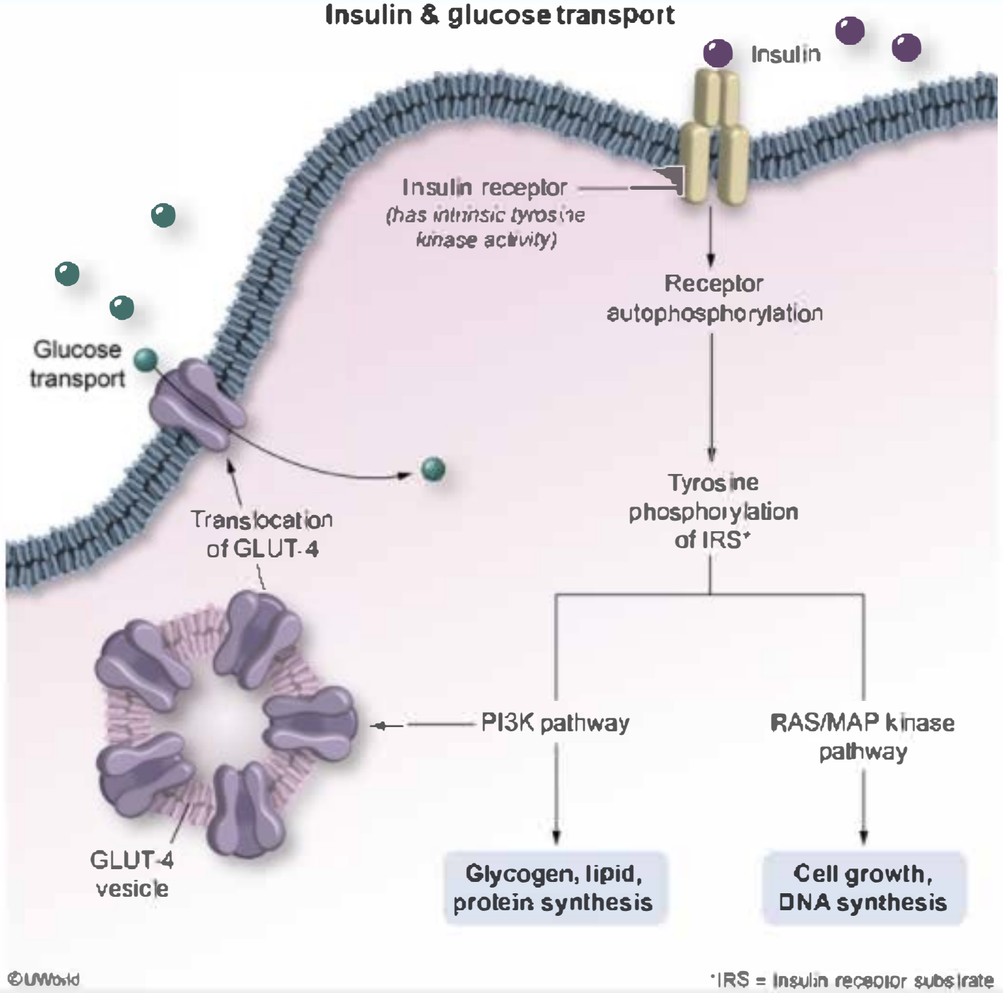
Exhibit Display

Insulin & glucose transport



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maintain glucose levels in the fasting state; increased activity would improve hypoglycemic symptoms by increasing circulating glucose levels.

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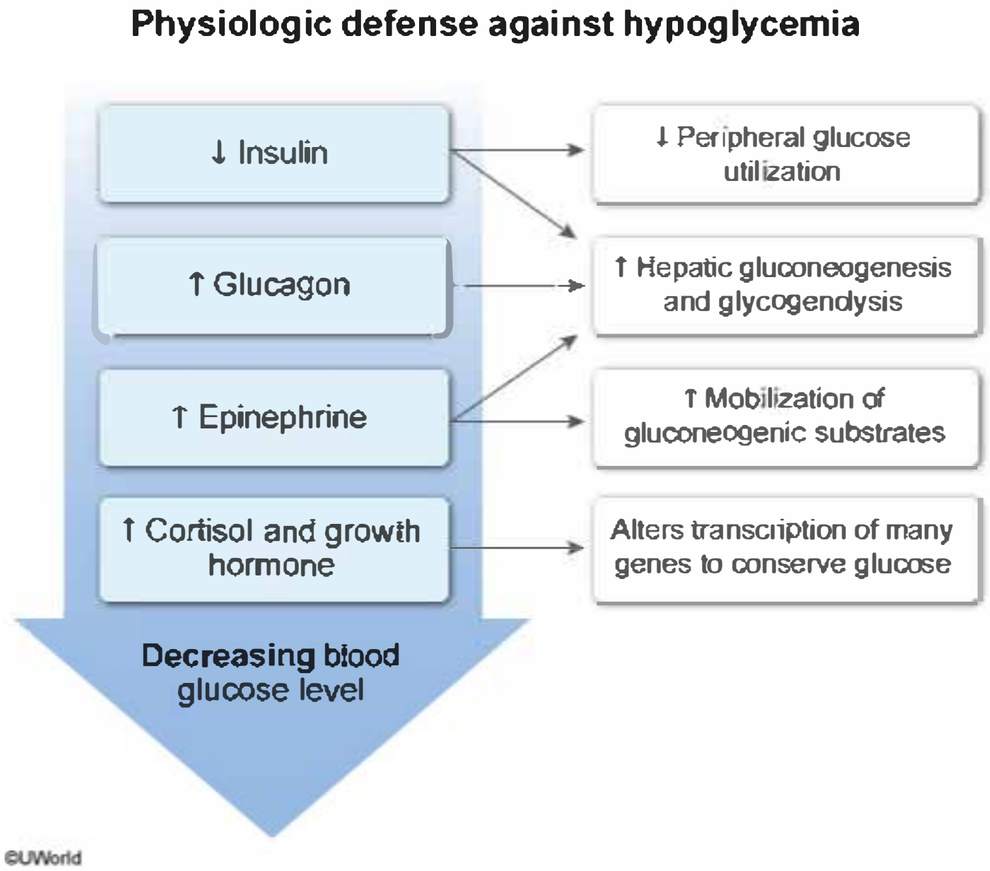

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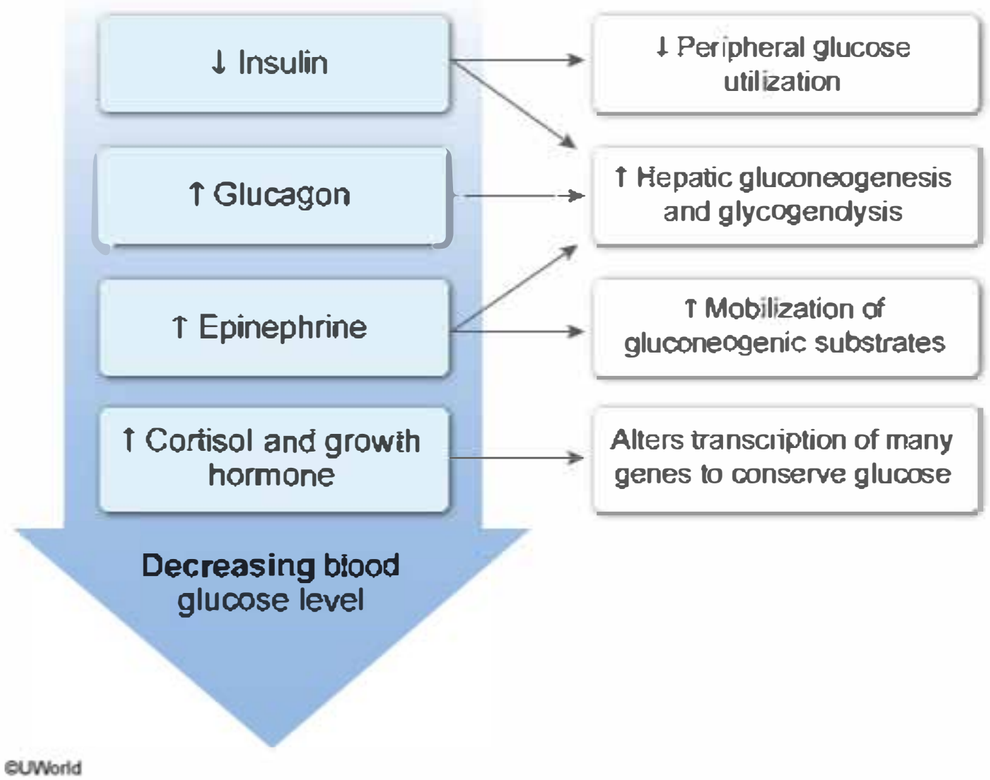
Exhibit Display

Physiologic defense against hypoglycemia



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References

- Exercise, GLUT4, and skeletal muscle glucose uptake.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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The circuit shown below has an inflow pressure of 120 mmHg and an outflow pressure of 40 mmHg.

Resistance in each of the four vessels shown is 2 mmHg/mL/min (R1 = R2 = R3 = R4 = 2 mmHg/mL/min). What is the total peripheral resistance of the circuit shown on the slide?

A. 8 mmHg/ml/min

B. 4 mmHg/ml/min

C. 2 mmHg/ml/min

D. 1 mmHg/ml/min

E. 0.5 mmHg/ml/min

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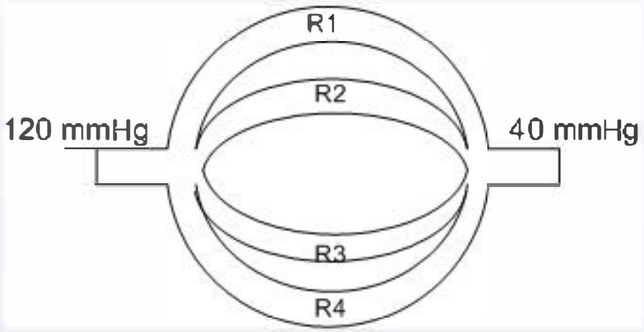
The circuit shown below has an inflow pressure of 120 mmHg and an outflow pressure of 40 mmHg.



Resistance in each of the four vessels shown is 2 mmHg/mL/min (R1 = R2 = R3 = R4 = 2 mmHg/mL/min). What is the total peripheral resistance of the circuit shown on the slide?

A. 8 mmHg/ml/min

B. 4 mmHg/ml/min

C. 2 mmHg/ml/min

D. 1 mmHg/ml/min

E. 0.5 mmHg/ml/min

Submit

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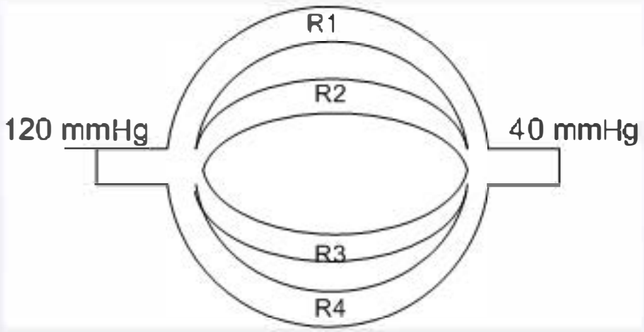
The circuit shown below has an inflow pressure of 120 mmHg and an outflow pressure of 40 mmHg.



Resistance in each of the four vessels shown is 2 mmHg/mL/min (R1 = R2 = R3 = R4 = 2 mmHg/mL/min). What is the total peripheral resistance of the circuit shown on the slide?

A. 8 mmHg/ml/min (13%)

B. 4 mmHg/ml/min (4%)

C. 2 mmHg/ml/min (30%)

D. 1 mmHg/ml/min (2%)

✓ E. 0.5 mmHg/ml/min (48%)

Omitted
Correct answer
E

48%
Answered correctly

03 secs
Time Spent

02/03/2020
Last Updated

Explanation

3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33

Explanation

The diagram given in the question stem illustrates a set of vessels arranged in parallel. Systemic circulation is often simplified in this way for the purposes of calculating total peripheral resistance (TPR). Each branch of the aorta can be visualized as one of the vessel branches on the above graph. For example, the four vessels above could represent coronary, splanchnic, renal, and cerebral circulation. The formula for calculating the total restistance for parallel circuits is as follows. RT represents total peripheral resistance, and the circuits represent blood vessels.

$1/R_T = 1/R1 + 1/R2 + 1/R3 + \ldots 1/Rn$

In this calculation, the inverse of the TPR (or RT) is equal to the sum of the inverse of each vessel or system that lies in parallel. The resistance of the vessels are R1 = R2 = R3 = R4 = 2 mmHg/ml/min. Therefore

$1/TPR = ½ + ½ + ½ + ½ = 4(½) = 2$
so $TPR = ½ = 0.5$

Therefore, the TPR = ½ or 0.5 mmHg/ml/min.

(Choice A) Eight (8) mmHg/ml/min would be the resistance if each of the above vessels were arranged in series, rather than in parallel. A series arrangement does not estimate total body circulation well, but is a good way to describe blood flow in an individual organ. To calculate the resistance of a circuit in series, the individual values for resistance are summed as follows:

Total resistance in organ = $R_{artery} + R_{arteriole} + R_{capillary} + R_{venule} + R_{vein}$

Educational Objective:
The total resistance for a group of vessels arranged in parallel is equal to one divided by the sum of the inverse values for resistance of each of the contributing vessels as follows: $1/TPR = 1/R1 + 1/R2 + 1/R3 + \ldots 1/Rn$. Total body circulation can be best described as a parallel circuit, whereas circulation in an individual organ is often best described by a series arrangement.

Physiology General Principles Total peripheral resistance